

Advances in
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CHEMISTRY

Edited by

A. R. KATRITZKY

*School of Chemical Sciences
University of East Anglia
Norwich, England*

Assistant Editors

A. J. BOULTON

*University of East Anglia
Norwich, England*

J. M. LAGOWSKI

*The University of Texas
Austin, Texas*



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Contributors

Numbers in parentheses indicate the pages on which the authors' contributions begin.

ADRIEN ALBERT, *Department of Medical Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, Australia* (1)

W. L. F. ARMAREGO, *Department of Medical Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, Australia* (1)

H. J. DEN HERTOEG, *Laboratory of Organic Chemistry of the Agricultural University, Wageningen, The Netherlands* (121)

JAMES L. FEDRICK, *Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York* (145)

ROBERT FILLER, *Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois* (75)

D. D. PERRIN, *Department of Medical Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, Australia* (43)

ROBERT G. SHEPHERD, *Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York* (145)

R. SLACK, *The Research Laboratories, May and Baker Ltd., Dagenham, Essex, England* (107)

H. C. VAN DER PLAS, *Laboratory of Organic Chemistry of the Agricultural University, Wageningen, The Netherlands* (121)

K. R. H. WOOLDRIDGE, *The Research Laboratories, May and Baker Ltd., Dagenham, Essex, England* (107)

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Preface

Four of the chapters in this the fourth volume of *Advances in Heterocyclic Chemistry* deal with topics which have never been reviewed before. The first simple isothiazole was studied by Dr. R. Slack in 1956, and he and Dr. K. R. H. Wooldridge review in their article the considerable progress which has been made since then. Similarly the discovery of the widespread occurrence of covalent hydration has been achieved by the Canberra School, and we now have authoritative reviews on the qualitative (Drs. A. Albert and W. L. F. Armarego) and quantitative (Dr. D. D. Perrin) aspects of covalent hydration. Following the realization of the importance of aryne intermediates in benzenoid chemistry, work has been done on hetarynes, and this field is now reviewed by Professor H. J. den Hertog and Dr. H. C. van der Plas who have themselves contributed much to this subject. The volume also includes a review of oxazolone chemistry by Dr. R. Filler and a survey of the reactions of azines with nucleophiles by Drs. R. G. Shepherd and J. L. Fedrick which complements the previous review by Professor Illuminati in Volume 3 of this series. The last chapter forms a very significant contribution to heterocyclic chemistry in correlating an enormous amount of data, scattered throughout the literature, on this important subject.

Suggestions for contributions to subsequent volumes of the series are welcomed; they should be submitted in the form of a short synopsis.

Thanks are due to the authors for their cooperation, the members of the Editorial Board, and the publishers. I am especially grateful to the assistant editors, Dr. A. J. Boulton and Dr. J. M. Lagowski, for all their help.

A. R. KATRITZKY

Norwich, England
March, 1965

Covalent Hydration in Nitrogen-Containing Heteroaromatic Compounds: I. Qualitative Aspects

ADRIEN ALBERT and W. L. F. ARMAREGO

*Department of Medical Chemistry, Institute of Advanced Studies,
The Australian National University, Canberra, Australia*

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I. Introduction

The addition of water across carbon-carbon double bonds, a reaction thoroughly investigated by Lucas¹ and Taft,² requires strong activation and is catalyzed by hydrogen ions and hydroxyl ions. Addition of water across the C=O bond of aldehydes has also been studied kinetically.³ Whereas chloral and formaldehyde are largely hydrated (at equilibrium in dilute aqueous solution), acetaldehyde and other

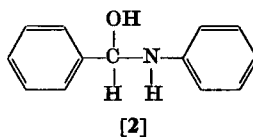
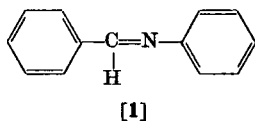
¹ H. J. Lucas, W. T. Stewart, and D. Pressman, *J. Am. Chem. Soc.* **66**, 1818 (1944).

² R. W. Taft, *J. Am. Chem. Soc.* **74**, 5372 (1952).

³ R. P. Bell and B. deB. Darwent, *Trans. Faraday Soc.* **46**, 34 (1950).

saturated aliphatic aldehydes are only about 50% hydrated under these conditions. The hydration reaction, which gives 1,1-glycols, is catalyzed in both directions by hydrogen ions and hydroxyl ions⁴ and requires little activation.

No comparable study of the hydration of the C=N bond has been made although its properties lie between those of the C=C and C=O bonds. The hydration of Schiff bases, such as benzylideneaniline (**1**), to cations of Dimroth bases, such as **2**, is well-known, but attempts to follow this reaction kinetically have been frustrated by the ready breakdown of the neutral species, e.g. **2**, to benzaldehyde and aniline. About ten years ago, workers in this Department were surprised to find the C=N bond in many pteridines is capable of hydration, analogous to the reaction $1 \rightleftharpoons 2$. The surprise stemmed principally



from the apparent loss of aromaticity upon hydration. What is still more surprising is that hydration of the C=N bond in nitrogen-containing heterocyclic compounds is not, as a rule, followed by fission of the C—N bond. These properties and their probable causes are discussed in this review.

The phenomenon of C=N hydration in pteridines was first observed in this Department in 1951,⁵ although the correct interpretation was arrived at slowly.^{6, 7} The first example was discovered as a result of the very curious behavior of 6-hydroxypteridine during titration.⁵ With alkali, a curve is traced corresponding to a weak acid of pK_a 9.7. But, on back-titration with acid, this curve is not retraced; instead, a new curve appears corresponding to a much stronger acid of pK_a 6.7. It has been demonstrated^{5, 8} that ring-opening does not take place and that the change is not tautomeric. In 1955, it was recognized that 6-hydroxypteridine is covalently hydrated in water, whereas its anion

⁴ C. K. Ingold, "Structure and Mechanism in Organic Chemistry," p. 689. Bell, London 1953.

⁵ A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.* 1620 (1952).

⁶ A. Albert, *J. Chem. Soc.* 2690 (1955).

⁷ D. J. Brown and S. F. Mason, *J. Chem. Soc.* 3443 (1956).

⁸ A. Albert, in "The Chemistry and Biology of Pteridines" (G. E. W. Wolstenholme and M. P. Cameron, eds.), p. 204. Churchill, London, 1954.

is most stable in the anhydrous form.⁶ The hydrated neutral species is a weaker acid than the anhydrous species, hence the hysteresis loop shown in Fig. 1.

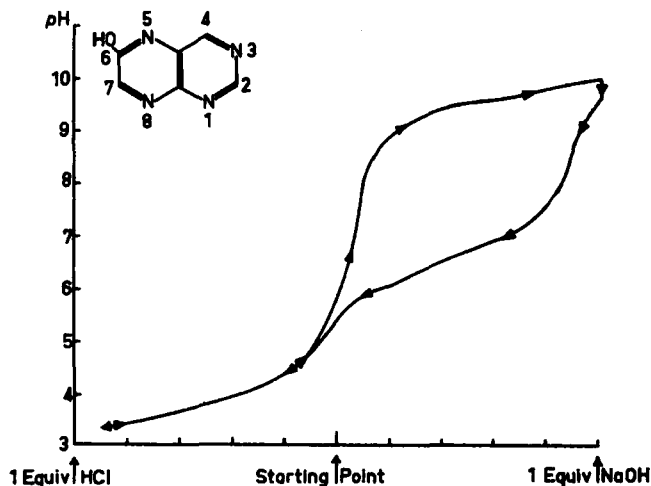
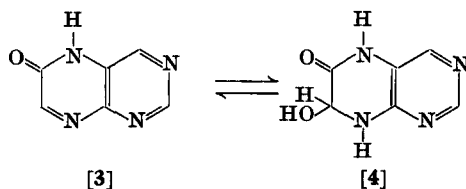


FIG. 1. Hysteresis loop produced when 6-hydroxypteridine is titrated with acid and alkali.

The water molecule was found to add across the 7,8-positions in 6-hydroxypteridine by Brown and Mason.⁷ These authors showed that the neutral species of 6-hydroxypteridine exists mainly as 6,7-dihydroxy-7,8-dihydropteridine (**4**) in equilibrium with a little of **3**. The stable cation is largely derived from **4** and the stable anion largely from **3**.



Following these discoveries, we have made an extensive experimental study of covalent hydration and find it is very common, not only in the pteridine series but also in several simpler families of polyanaphthalenes.⁹ The methods used to diagnose this phenomenon, its

⁹ A. Albert, in "Pteridine Chemistry" (W. Pfeleiderer and E. C. Taylor, eds.), p. 111. Pergamon Press, Oxford, 1964.

occurrence in the various heterocyclic families, factors in the stabilization of the covalent hydrates, ring-opening, and the chemical and biological implications are discussed in this review. Quantitative aspects are thoroughly covered by Dr. D. D. Perrin in the following review.¹⁰ Where we have introduced a quantitative technique, it has been at Dr. Perrin's suggestion. Whenever the word "hydrate" is used in this review, it refers to water bound covalently as in 4.

II. Diagnosis and Location of Covalent Hydration

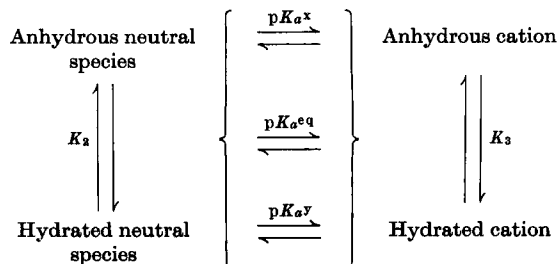
The choice of methods to diagnose covalent hydration in nitrogen-containing heteroaromatic compounds depends largely on the ratio of hydrated to anhydrous species at equilibrium in the cation, neutral species, or anion. This potentially complex situation is simplified in most cases because in one of two ionic species (e.g. cation and neutral species) the percentage of hydrate is usually comparatively small. Small as this percentage may be, it is never insignificant, because if marked hydration can be demonstrated in one ionic species, the equilibria involved (see equilibrium diagram in Section II, A) necessitate the presence of at least a trace of hydrate in the second ionic species. These minute percentages of hydrates influence the values of the equilibrium constants. For this reason the term "anhydrous" cannot be used in place of "predominantly anhydrous" when referring to a mixture containing $< 0.1\%$ of the hydrated species. The same argument pertains to the hydrated species, which must be in equilibrium with at least a very small amount of anhydrous species.

The following methods have been used to demonstrate a substantial degree of covalent hydration in the various ionic species. Usually, at least three of these methods have had to be applied before the phenomenon could be established beyond all doubt. Before enumerating these, it should be made clear that the presence or absence of strongly held water of crystallization is to be regarded as a competitive phenomenon which makes no contribution to a diagnosis of covalent hydration. Thus, 4,7-dihydroxy-6-methylpteridine, 2-hydroxypurine, and 4,5-diamino-2-hydroxypyrimidine all retain one molecule of water obstinately at 130° but give no indications of covalent hydration in any of the following tests. On the other hand, pteridine, which the tests show to be covalently hydrated to the extent of $\sim 22\%$ in solution, reveals no hydration upon elementary analysis after gentle drying at 20° .

¹⁰ D. D. Perrin, following review, p. 43.

A. ANOMALOUS IONIZATION CONSTANTS

It is a simple matter to determine an ionization constant and also to predict its magnitude.¹¹ When these values do not agree, and if ring-opening has been carefully excluded, the likelihood of covalent hydration must be considered. Equilibria encountered during the determination of the ionization constant of a hydrating heteroaromatic base are shown in the following diagram. Similar equilibria exist for

Equilibrium Diagram^{11a}

hydrating bases which have an acid function, e.g. the hydroxypteridines. K_a^x and K_a^y are the *ionization* equilibrium constants for the anhydrous and the hydrated species, respectively, and should be experimentally realizable if measurements could be made much more rapidly than the time required to record significant hydration and dehydration. (Where more than one basic center is present, these experimentally determined pK values might, theoretically, be capable of further analysis into so-called "microscopic" pK values.) K_2 and K_3 are *hydration* equilibrium constants¹⁰ which include the rates of hydration and dehydration of the neutral species and cation, respectively. If the equilibria K_2 and K_3 are set up rapidly (e.g. quinazoline) then the pK_a value obtained in a routine potentiometric or spectrometric determination is an overall value (denoted as pK_a^{eq}) which includes not only the hydration equilibria K_2 and K_3 but also the ionization constant of the anhydrous and hydrated species.

On the other hand, if the equilibria for K_2 and K_3 are attained slowly (see Fig. 1) and the optical density or pH readings are measured rapidly, either the pK_a^x or pK_a^y value can be obtained directly,

¹¹ A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases." Methuen, London, 1962.

^{11a} The ratios K_2 and K_3 are defined here so as to conform with the following review by Dr. D. D. Perrin.

depending on whether one starts from the predominantly anhydrous neutral species or the predominantly hydrated cation (or anion). However, if the solutions are allowed to come to equilibrium before each reading, only the pK_a^{eq} value can be obtained.

The pK_a^{eq} value always lies between the pK_a^x and pK_a^y values. Because aromatic or partly aromatic heterocyclic species, e.g. **3** (the concentrations of which are included in the pK_a^x expression), are weaker bases than the corresponding carbinolamines, e.g. **4** (the concentrations of which are involved in the pK_a^y expression), it follows that $pK_a^x < pK_a^y$. Because the anhydrous species is aromatic (or partly aromatic, if some of the conjugation may be in a $-\text{CO}.\text{NH}-$ group) the basic pK_a^{eq} value is always higher than that which would be predicted for the aromatic system, and the substance behaves as if it were a stronger base than expected (e.g. quinazoline¹²: found, 3.51; expected, ~ 1.5). Hydration should always be suspected when potentiometric readings, made during determinations of pK values, show a drift. The hydration-dehydration process is acid and base catalyzed,¹⁰ so if hydration is occurring, steady readings should be obtained progressively more rapidly as the hydrogen ion or hydroxyl ion concentration is increased. It must, however, be noted that reversible ring-opening after addition of water could show similar behavior, and other methods, described below, must be applied before hydration can be confirmed.

The constants pK_a^x , pK_a^{eq} , and pK_a^y are related in the following manner¹⁰:

$$K_2 = K_a^y(K_a^x - K_a^{\text{eq}})/K_a^x(K_a^{\text{eq}} - K_a^y),$$

$$K_3 = (K_a^x - K_a^{\text{eq}})/(K_a^{\text{eq}} - K_a^y),$$

where K_2 = (concentration of hydrated neutral species)/(concentration of anhydrous neutral species) and K_3 = [concentration of hydrated cation (or anion)]/[concentration of anhydrous cation (or anion)] at equilibrium. It is evident that K_2 and K_3 are independent of pH and dependent only on the three ionization constants. When base strengths are to be compared, only pK_a^x or pK_a^y values can be legitimately used, because only they are confined to pure species. If pK_a^{eq} values are compared, the results have no significance because K_2 and K_3 vary from one substance to another.

The above relationships can be used to calculate some of the con-

¹² A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.* 2689 (1961).

stants which cannot be obtained by direct measurement, e.g. accurate values of K_2 or K_3 .

It is presumptuous to report that a substance is not hydrated simply because there are no drifts in the readings obtained during potentiometric measurements or because the experimentally determined pK_a value is not very different from the predicted value. A small amount of hydration may cause only a small difference in the ionization constant and hence other tests should be applied. A number of heterocyclic compounds which have seemingly normal pK_a values may well be partially hydrated.

B. ELECTRONIC (ULTRAVIOLET AND VISIBLE) ABSORPTION SPECTRA

Addition of water across a C=N bond in a conjugated system breaks the conjugation and alters the electronic transitions. The ultraviolet and visible spectra of anhydrous and hydrated species are therefore usually dissimilar, and such differences have been used as the basis for much of the qualitative and quantitative work done on covalent hydration.

1. Spectra in Hydrocarbons and Dilute Aqueous Solutions

The spectra of an organic compound in various solvents differ only in small detail so long as no serious interaction takes place between solute and solvent. Thus the spectrum of a substance in an aprotic solvent (e.g. cyclohexane) should be almost the same as that in water. When addition of water occurs across a C=N bond, the spectrum of the hydrate in water can be vastly different from the spectrum of the anhydrous substance in cyclohexane, and this test has been used on several occasions¹²⁻¹⁶ to determine whether or not a neutral species forms a hydrate in water. The test, however, is not valid if (a) the solute possesses the elements of water in the crystalline state, (b) the amount of hydrated species in aqueous solution is too small to cause any noticeable differences in the spectra,¹³ or (c) the principal pathway of electronic transition in the molecule involves no affected bond.

Protonation of heteroaromatic compounds is known to produce only small shifts ($\pm 5 m\mu$) of the long-wave length band present in the case

¹³ W. L. F. Armarego, *J. Chem. Soc.* 561 (1962).

¹⁴ W. L. F. Armarego, *J. Chem. Soc.* 4094 (1962).

¹⁵ W. L. F. Armarego, *J. Chem. Soc.* 4303 (1963).

¹⁶ W. L. F. Armarego, *J. Chem. Soc.* 5030 (1962).

of the neutral species. On the other hand, if the cation is much more hydrated than the neutral species, these shifts (which may be hypsochromic or bathochromic) are normally larger than can be accounted

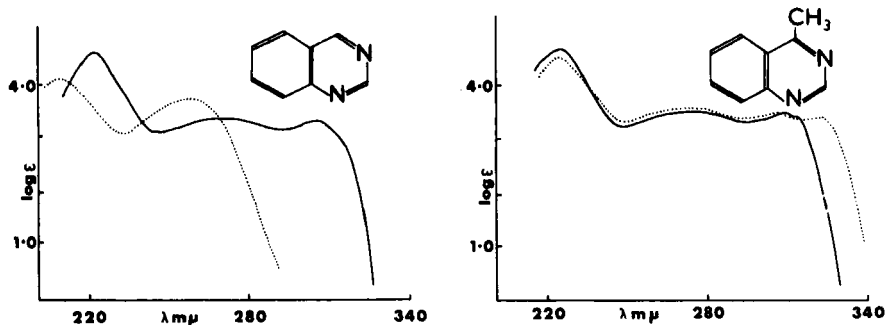


FIG. 2. (A) Ultraviolet spectra of quinazoline in water. Solid line, neutral species; dotted line, cation. (B) Ultraviolet spectra of 4-methylquinazoline in water. Solid line, neutral species; dotted line, cation.

for by protonation alone. Quinazoline, for example, shows a hypsochromic shift of $45 \text{ m}\mu$ ¹² (see Fig. 2A), whereas 1,4,5,8-tetraazanaphthalene shows a bathochromic shift of $20 \text{ m}\mu$ (see Fig. 3).¹⁶ For a few substances, e.g. pteridine and the *Bz*-nitroquinazolines, however,

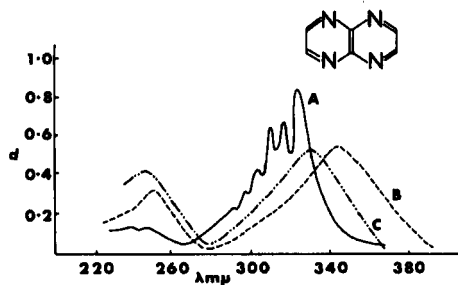
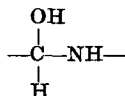


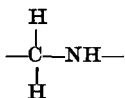
FIG. 3. Ultraviolet spectra of 1,4,5,8-tetraazanaphthalene in water. (A) Anhydrous neutral species, (B) hydrated cation, and (C) hydrated neutral species.

these spectral differences between the anhydrous and hydrated species are small. Similarly, for compounds with an acidic function and where the anions are predominantly anhydrous and the neutral molecules strongly hydrated, e.g. 2- and 6-hydroxypteridine,⁷ large spectral differences between the anion and the neutral species are readily

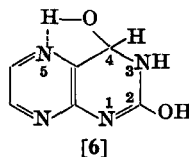
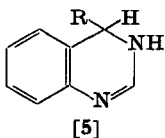
observed (see Table I in ref. 10). The direction of these shifts depends largely on the new chromophore formed after hydration, but is usually similar for members of a family of compounds provided that hydration occurs in the same position, e.g. across the 3,4-double bond in quina-zolines.¹³ The virtual optical transparency of an alcoholic hydroxyl group should make the spectra of the hydrates, which possess the



group, similar to those of the corresponding dihydro compounds, which contain the



group. One of the first pieces of evidence which indicated the correct positions of water addition in 2- and 6-hydroxypteridine was the similarity between the spectra of the "hydrates" and the corresponding dihydrohydroxypteridines^{7,18} (see Table I, e.g. Nos. 7 and 8). However, this is not always the case, because there is a difference of 26 m μ between the long-wavelength bands of the neutral species of hydrated quinazoline (5; R = OH) and of 3,4-



dihydroquinazoline (5; R = H).¹⁹ The spectra of other dihydroquinazolines such as 5 (R = SO₃H, Me, and CN) differ only slightly from that of 5 (R = H), and the reason for the anomalous difference when R = OH may perhaps be explained by a hydrogen-bonding interaction between the hydroxyl group and the π -orbital of the benzene ring. Hydrogen bonding of a somewhat different kind can occur in hydrated 2-hydroxypteridine (6) between the hydroxyl group and the N-5 position, and the difference in the positions of the long-wavelength bands in the spectra of 6 and 3,4-dihydro-2-hydroxypteridine is 10 m μ and for the corresponding 6-methyl derivatives only 6 m μ (see Table I). Thus the expected similarity between the spectra of a hydrate and the corresponding dihydro derivative can vary

considerably in different ring systems and to a lesser degree in the same ring system.

TABLE I
COMPARISON OF THE SPECTRA OF SOME HYDRATES AND THOSE OF THE RELATED DIHYDRO DERIVATIVES^a

No.	Compound	$\lambda_{\max}(\text{m}\mu)^b$	$\log \epsilon^b$	Ref.
1	2-Hydroxypteridine (hydrate)	230; 307	3.88; 3.83	7
2	3,4-Dihydro-2-hydroxypteridine	248; 317	3.72; 3.89	17
3	7,8-Dihydro-2-hydroxypteridine	223; 290	4.35; 3.88	17
4	2-Hydroxy-6-methylpteridine (hydrate)	235; 315	4.05; 3.93	17
5	3,4-Dihydro-2-hydroxy-6-methylpteridine	248; 321	3.83; 3.92	17
6	7,8-Dihydro-2-hydroxy-6-methylpteridine	220; 287	4.46; 3.99	17
7	6-Hydroxypteridine (hydrate)	<u>266</u> ; 289	<u>3.85</u> ; 4.00	7, 18
8	7,8-Dihydro-6-hydroxypteridine	<u>275</u> ; 293	<u>3.80</u> ; 3.93	7, 18
9	Quinazoline (hydrate)	265	3.97	19
10	3,4-Dihydroquinazoline	221; 291	4.09; 3.76	19

^a Ultraviolet spectra in water for neutral species. The spectral differences between the hydrated cations and the cations of the corresponding dihydro derivatives are of the same magnitude as those observed between the neutral species.

^b Underlined values indicate inflection.

2. Spectra in Concentrated Aqueous Sulfuric Acid

By increasing the concentration of sulfuric acid in water, the thermodynamic activity of the water can be strongly decreased. If the acidity of a solution of a predominantly (or partly) hydrated cation is progressively increased, the amount of free water remaining in the medium for hydration of the organic molecule is correspondingly decreased, and the spectrum thus becomes more similar to that of the anhydrous cation. In quinazoline, for example, bands present in the 271 and 305 $\text{m}\mu$ region at pH 7, which are associated with the predominantly anhydrous neutral species, disappear at pH 1 (because the hydrated cation is formed) but reappear on increasing the acidity to $H_0 - 3.5$ (because the anhydrous monocation is formed).¹² A similar effect is observed with quinazoline 3-oxide¹⁶ (see Fig. 4) and 3-nitro- and 8-

¹⁷ A. Albert and S. Matsuura, *J. Chem. Soc.* 5131 (1961).

¹⁸ A. Albert and F. Reich, *J. Chem. Soc.* 127 (1961).

¹⁹ A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.* 5267 (1961).

nitro-1,6-naphthyridine.²⁰ If the shifts obtained by increasing the acidity are not too large, well-defined isosbestic points can be observed (Fig. 4). Hydrochloric acid at similar H_0 values produces the same dehydrating effect.¹⁶ This application is limited to substances that do not react with the strong acid (e.g. by sulfonation, or even forming dications).

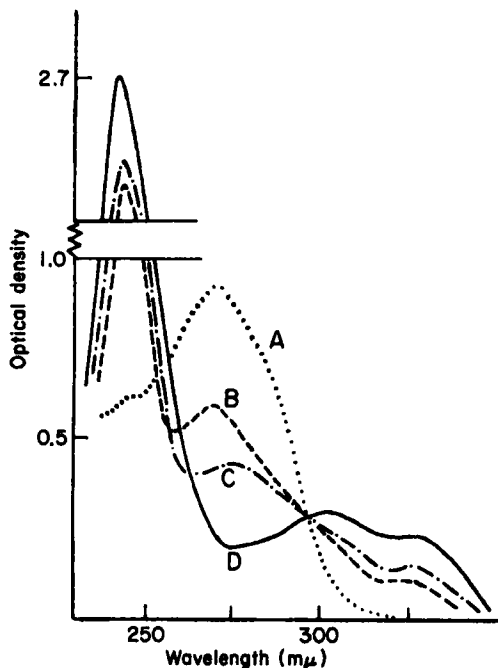


FIG. 4. Effect of acidity (strong solutions of H_2SO_4) on the spectrum of quinazoline 3-oxide. (A) $H_0 - 1.12$; (B) $H_0 - 2.06$; (C) $H_0 - 4.40$; (D) $H_0 - 5.65$.

3. Spectra in Anhydrous Dichloroacetic Acid

The spectral changes which occur in increasingly acid solutions of polyaza-heterocycles may indicate a second ionization. This event, however, can readily be distinguished from dehydration by measuring the spectra in anhydrous dichloroacetic acid, provided that the pK_a value for the anhydrous species is above 1. Anhydrous dichloroacetic acid has a Hammett acidity function (H_0) of -0.9 (as determined using *o*-nitroaniline as the solute),¹² and the ultraviolet spectrum of a base with a $pK_a > 1$ would be that of the anhydrous cation in this

²⁰ A. Albert and W. L. F. Armarego, *J. Chem. Soc.* 4237 (1963).

solvent. If the pK_a is not much greater than 1, the spectrum must be that of the *monocation*. Comparison of the spectrum measured in this solvent with that determined in dilute aqueous acid has been used to confirm covalent hydration in quinazoline¹² and in a number of 2-aminopteridines.²¹

Another use for this solvent is exemplified by 1,4,5,8-tetraazanaphthalene,¹⁵ the anhydrous species of which has a predicted pK_a value of -2.7 (the observed pK_a in water is $+2.51$). The spectrum obtained in anhydrous dichloroacetic acid is almost identical with that of the predominantly anhydrous neutral species determined in water, but quite different from the spectrum measured in dilute aqueous acid. Moreover, addition of water to the anhydrous dichloroacetic acid solution of this base caused the fine structure present in the spectrum of the neutral species to disappear and the band due to the hydrated cation (i.e. the spectrum obtained in water at pH 0.5) to appear. Addition of water to dichloroacetic acid solutions has been used to show that the cations of 3- and 8-nitro-1,6-naphthyridine²⁰ are hydrated in aqueous acid at pH 0.5.

The application of this method is limited by the opacity of dichloroacetic acid below $\sim 305\text{ m}\mu$. However, most of the shifts that are significant for detecting hydration are those of long-wavelength bands, usually above $300\text{ m}\mu$, so this limitation is not serious. When a cation has a very strong affinity for water, a mere trace of water in the dichloroacetic acid will give a mixed spectrum. Careful purification of the dichloroacetic acid and strict exclusion of water during the measurements are necessary to obtain the spectrum of the anhydrous species.²¹ Other suitable acids (e.g. $\text{CF}_3\text{CO}_2\text{H}$) could be used in place of $\text{CHCl}_2\text{CO}_2\text{H}$.

Similarly a suitable optically transparent anhydrous (strong) base, e.g. piperidine, could be used to obtain the spectra of anhydrous anions.

C. "BLOCKING EFFECT" OF A METHYL GROUP

One of the most valuable means for locating the site of hydration involves the "blocking effect" of a methyl group.

Insertion of a methyl group at the site where nucleophilic attack (by OH^- or H_2O) occurs during hydration considerably hinders the addition of water, thus lowering the percentage of the hydrated

²¹ A. Albert, C. F. Howell, and E. Spinner, *J. Chem. Soc.* 2595 (1962).

species present at equilibrium (cf. Table IV of ref. 10) (there is also a decrease in the rate of hydration and an increase in the rate of dehydration).²² This effect, although partly electronic, has been shown to be largely steric^{12, 18} and apparently is caused by steric acceleration of the elimination of the hydroxyl group.²² It is closely related to the well-established steric nature of the opposition to addition of Michael reagents across a C=C bond, shown by a methyl group attached to that carbon atom which attracts the nucleophilic Michael anion.⁴

Thus, a methyl group placed at the site of hydration decreases the proportion of the hydrated species and, hence, shifts both the ultra-violet spectra (cf. Fig. 2A and B) and the ionization constant of the substance towards normality. A valuable means for locating the site of hydration, therefore, is to introduce a methyl group in various likely places until the anomalous spectrum is lost and the spectrum of the predominantly anhydrous species restored. The effect of such a methyl group on the pK_a value is also revealing because a decrease in the amount of the hydrated species causes a decrease in the pK_a value, whereas a methyl group is otherwise base-strengthening. The "blocking effect" of a methyl group has been used to locate the hydration site where nucleophilic attack occurs in 2-hydroxy-,²³ 6-hydroxy-,¹⁸ and 2-amino-pteridines²¹; in quinazolines¹²; quinazoline 3-oxides¹⁶; and 1,4,5,8-tetra-azanaphthalenes.¹⁵ So far no example is known with certainty in which a methyl group suppresses hydration entirely.

D. MILD OXIDATION

Heterocyclic compounds that have water bound covalently across a C=N bond behave as secondary alcohols. When subjected to very gentle oxidative conditions, they are converted into the corresponding oxo compounds. Potassium permanganate⁷ in 0.1*N* sodium hydroxide at room temperature has been used to oxidize 2- and 6-hydroxypteridine to 2,4- and 6,7-dihydroxypteridine, respectively. In contrast, 4-hydroxypteridine⁷ was not attacked by this reagent even at 100°. Hydrogen peroxide in acid solution was used to oxidize quinazoline¹²; quinazoline 3-oxide¹⁶; 1,3,5-, 1,3,7-, and 1,3,8-triazanaphthalene¹⁴; and pteridine²⁴ (which hydrate across the 3,4-double bond in the

²² Y. Inoue and D. D. Perrin, *J. Chem. Soc.* 4803 (1963).

²³ A. Albert and C. F. Howell, *J. Chem. Soc.* 1591 (1962).

²⁴ D. D. Perrin, *J. Chem. Soc.* 645 (1962).

cations). The pH of the solution was adjusted so as to ensure the formation of the maximum amount of the hydrated species, and not more than two equivalents of the reagent were used. Hydrogen peroxide, although not completely specific for carbinolamines, has the advantage of being optically transparent, and the oxidations can thus be followed spectrophotometrically¹⁴ using only small amounts of material. Potassium ferricyanide has been successfully used for similar oxidations in the 1,4,6-²⁵ and 1,4,5-triazanaphthalene²⁶ series.

The principal use of this oxidative test for hydration is to locate quickly the probable site of hydration, which can then be confirmed by inserting a methyl group as described in Section II, C.

The above method is unsatisfactory when hydration takes place at two alternative sites in the molecule, although one hydrate is usually present in only a very small proportion, at equilibrium. Which oxo compound is preferentially formed in such a case depends on the rates of oxidation at the different sites and on the rate of isomerization of the water molecule from one position to the other, hence this method does not indicate which is the thermodynamically more stable hydrate.

Occasionally it happens that the oxo compound, produced by oxidation, forms a hydrate which is further oxidized to a dihydroxy compound.¹⁵ Attention must be given to the possibility (so far unreported) that when the hydrated species is in equilibrium with a trace of the ring-opened structure a sufficiently fast oxidation rate of the amino-aldehyde (i.e. the acyclic structure) could lead to the incorrect conclusion that the original material was not cyclic.

E. RAPID-REACTION TECHNIQUE

Because this technique and the apparatus involved are considered in detail in the following review,¹⁰ only a qualitative discussion is given here. This is the most valuable method for the confirmation of covalent hydration because it can usually give conclusive results even when the percentage of the hydrated species is as low as 2%. It makes use of the facts that all known examples of the formation or disappearance of the hydrated species followed first-order kinetics and that the rates are both acid- and base-catalyzed.¹⁰ It also depends on the usual state of affairs that the ratio of the hydrated to the anhydrous species, although pH independent (see Section II, A), is different in the three species, i.e. in the cation, neutral species, and anion. In principle, a solution of one

²⁵ A. Albert and G. B. Barlin, *J. Chem. Soc.* 5156 (1963).

²⁶ A. Albert and G. B. Barlin, *J. Chem. Soc.* 5737 (1963).

species (e.g. the neutral species) is rapidly converted (in less than one second, using a rapid-reaction apparatus¹⁰) into the other species (i.e. cation or anion) by mixing with a suitable buffer and then stopping the flow immediately (this is known as the *stopped-flow* technique). The rate of change of optical density is observed at a fixed and suitable wavelength. If both species, i.e. before and after mixing, are anhydrous, then, because protonation and deprotonation are practically instantaneous, no change in optical density should be observed after mixing. However, if covalent hydration is present (i.e. the ratio of the hydrated to anhydrous species is different before and after mixing), after mixing there should be a rate of change of optical density corresponding to an increase or decrease of the hydrated or anhydrous species, or *vice versa*. From the observed rate, the half-life of the hydrated species can be determined at the final temperature and pH value.

If one of the species is predominantly hydrated (e.g. the quinazoline cation^{13, 19}), then, by using the rapid-reaction apparatus and allowing an acid solution of the substance and a near-neutral buffer to run through the cell continuously (*continuous-flow* technique¹⁰), the spectrum of the predominantly hydrated (unstable) neutral species can be obtained. This is possible if the newly formed species is not too unstable.

For the determination of pK_a^x and pK_a^y (see Section II, A), a solution of one of the species (e.g. hydrated 2-hydroxypteridine)^{27a} is rapidly mixed with several alkaline buffers, and the rate of change of optical density (d_o) in the different buffers is extrapolated to zero time. The optical density (d_o) is a measure of the concentration of the hydrated anion at the moment, and pH, of mixing. A plot of d_o against pH therefore gives the value of pK_a^y . This value can be determined quite accurately because in the pH region of the buffers used (usually 3–11) the rates are slow enough to give reliable readings of d_o .²⁵ In the same way, but starting with the anhydrous anion of 2-hydroxypteridine, reliable values of the acidic pK_a^x have been determined. From a knowledge of pK_a^x , pK_a^{eq} , and pK_a^y for the acidic function, the ratio of the hydrated to the anhydrous species in the anion and the neutral molecule have been calculated. Outside the favorable pH range, the reactions are greatly accelerated and are often too fast for measurement in the apparatus described.

The basic pK_a^y values of the hydrated species have been measured

^{27a} D. D. Perrin and Y. Inoue, *J. Phys. Chem.* **66**, 1689 (1962).

for quinazoline,¹⁹ *Bz*-substituted nitroquinazolines, and 1,3,5-, 1,3,7-, and 1,3,8-triazanaphthalene.¹⁴ These values are in the favorable pH region (see above); however, accurate basic pK_a^x values for the anhydrous species could not be obtained because these values lie below 2 and hence the rate measurements fall in a region where they are too fast to give reliable values of d_o . In such cases, the ratio of the hydrated to the anhydrous species can be calculated for the neutral species, but not for the cation. 1,4,6-Triazanaphthalene is the only substance for which a pK_a^x value has been determined^{27b}; this was possible because the value (3.05) is in the favorable pH region.

Another disadvantage found in trying to apply this technique to very weak bases (i.e. those with $pK_a < 1$) is that the neutralization of strong acid solutions forms large quantities of salt and liberates much heat, which constitutes two sources of error.

F. ISOLATION OF HYDRATES AND HYDRATED SALTS

As is pointed out in the introduction to Section II, the presence or absence of water in the solid state gives no indication as to whether or not covalent hydration occurs in aqueous solution. However, many examples are known of substances which hydrate strongly in solution and also in the solid state. Thus, 2-hydroxy- and 6-hydroxy-pteridine crystallize with one molecule of water. On heating, the former loses water rapidly only at 180°, ²³ whereas the latter retains all of the water up to 180° where it begins to darken.⁶

Anhydrous quinazoline hydrochloride¹² absorbs one molecule of water readily, and the product is difficult to dehydrate completely even in a high vacuum at 60°. Infrared spectral data suggest that this water is covalently bound because of (a) the absence of several bands in the spectrum of the hydrate which are present in the spectrum of the anhydrous hydrochloride and (b) the presence of extra bands at 1474 and 1240 cm^{-1} that have been attributed to C—H and O—H bending vibrations of the —CHOH group.

Brown and Mason⁷ converted the hydrates into alcoholates by boiling them with alcohol. The hydrate and alcoholate of 6,7-diethyl-2-hydroxypteridine showed two N—H absorption bands in the infrared, and, when either compound was heated at 120° *in vacuo*, the band of higher frequency was strongly reduced in intensity. These results led to a new test for covalent hydration: the substance is refluxed with

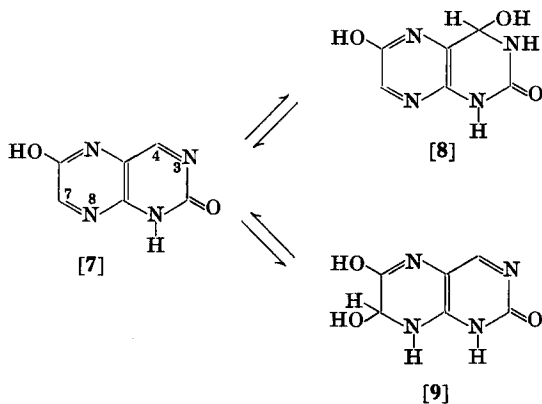
^{27b} D. D. Perrin and Y. Inoue, *Proc. Chem. Soc.* 342 (1960).

methanol or ethanol for 24 hr, and the product is examined (a) by elemental analysis to determine if one molecule of water has been replaced by one of alcohol and (b) by paper chromatography to see if the R_f value of the product has changed, as it must do when covalently bound water is replaced (e.g. in 2- and 6-hydroxypteridine).²³

For a discussion of the use of polarography and nuclear magnetic resonance spectroscopy to detect covalent hydration, see the following review.¹⁰

G. CONSECUTIVE HYDRATIONS

When two sites of hydration are favored in a molecule (see Section IV for the influences involved), occasionally the relative rates of hydration are such that the first hydrate formed is not the more stable one. Thus 2,6-dihydroxypteridine (7) adds water first across the 3,4-position to give substance 8, but hydration across the 7,8-position takes place so effectively that after 2 hr most of the material is present as the isomer (9). The latter substance is the more stable but its formation involves overcoming a higher energy barrier.²⁸



6-Hydroxy-7-methylpteridine (neutral species) is hydrated in the 7,8-position, but it is transformed by hot, dilute acid into what appears to be an isomer in which water occupies the 3,4-position; the water is liberated by alkali from the latter isomer at a measurable rate to give the anhydrous anion common to both species.¹⁸

²⁸ A. Albert, Y. Inoue, and D. D. Perrin, *J. Chem. Soc.* 5151 (1963).

III. Occurrence of Covalent Hydration in Heteroaromatic Substances

A. GENERAL DISCUSSION

Covalent hydration has not been demonstrated in heteroaromatic compounds containing only one hetero atom, nor in systems which possess other hetero atoms in addition to nitrogen. The ready addition of nucleophilic reagents (e.g. acetylacetone, ethyl malonate, the cyanide ion, and Grignard reagents) to substances which are readily hydrated such as 2-hydroxypteridine,²¹ 6-hydroxypteridine,¹⁸ quinazoline,¹⁹ and quinazoline 3-oxide^{28a} always takes place across the same C=N bond to which the water molecule adds. Hence it might be expected that other heteroaromatic compounds which readily form adducts (e.g. acridine,^{29, 30} quinoxaline,³¹ and even, perhaps, quinoline³²) would form covalent hydrates. However, no hydration could be demonstrated in these substances nor in cinnoline or phthalazine, perhaps because water is a weak nucleophile. It is always possible that by using a more rapid or a more sensitive technique hydration may be detected in these substances as well as in a wide range of others.

Covalent hydration has been demonstrated in the following families of compounds: 1,6-naphthyridines, quinazolines, quinazoline 3-oxides, four families of 1,3,x-triazanaphthalenes, both 1,4,x-triazanaphthalenes, pteridines and some other tetraazanaphthalenes, and 8-azapurines; these compounds are discussed in that order. In general, for any particular compound (e.g. 6-hydroxypteridine) the highest ratio of the hydrated to the anhydrous species follows the order: cation > neutral species > anion. In some cases, however, anion formation is possible only when the species are hydrated, e.g. pteridine; cf. **21** and N-methyl-hydroxypteridines (Section III, E, 1, d). Table V in ref. 10 should be consulted for the extent of hydration in the substances discussed here.

B. NAPHTHYRIDINES

The physical properties of four of the six possible naphthyridines have been examined in some detail,³³ and hydration could not be demonstrated in the neutral species and cations of 1,5-, 1,6-, 1,7-, and

^{28a} T. Higashino, *Chem. Pharm. Bull* (Tokyo) **9**, 635 (1961).

²⁹ K. Lehmstedt and E. Wirth, *Ber.* **61**, 2044 (1928).

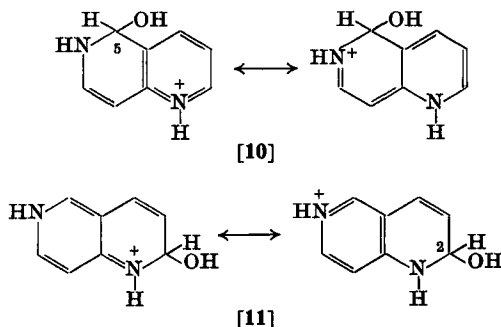
³⁰ F. Kröhnke and H. Honig, *Ann. Chem.* **624**, 97 (1959).

³¹ F. W. Bergstrom and R. A. Ogg, *J. Am. Chem. Soc.* **53**, 245 (1931).

³² F. W. Bergstrom and S. H. McAllister, *J. Am. Chem. Soc.* **52**, 2845 (1930).

³³ A. Albert, *J. Chem. Soc.* 1790 (1960).

1,8-naphththyridine. The principal evidence against hydration was the similarity between the ultraviolet spectra measured in cyclohexane, in water at near neutral pH, and in dilute aqueous acid. The ionization constants also showed no apparent anomaly. 1,6-Naphththyridine is of particular interest because water could add at two different sites, 5,6- (**10**) or 1,2- (**11**), to form cations which are stabilized by resonance (see Section IV for a discussion of this factor in stabilization). However,



when this substance was examined by rapid-reaction techniques the absence of hydration was confirmed.²⁰ The relatively positive nature (see Section IV) of C-2 and C-5 seems to be responsible for the absence of hydration. This has been demonstrated by a study of 3-nitro- and 8-nitro-1,6-naphththyridines in which the electron-deficiency on C-2 and C-5 in 1,6-naphththyridine is reinforced. The neutral molecules of both nitro compounds are predominantly anhydrous, but the cations are largely hydrated. The anomalous behavior of the cations was revealed by ultraviolet spectroscopy. Spectra determined in strong sulfuric acid and anhydrous dichloroacetic acid indicated that water-addition was involved, and using rapid-reaction techniques the presence of the unstable hydrated neutral species was detected.²⁰ Hydration was absent from both the neutral species and the cation of 3-nitro-1,5-naphththyridine.

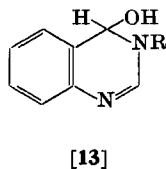
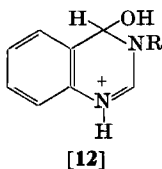
C. QUINAZOLINES

Hydration in quinazolines has been discussed in an earlier review³⁴ and will be only briefly reported here. Recent findings are considered in more detail.

³⁴ W. L. F. Armarego, in "Advances in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. I, p. 253. Academic Press, New York, 1963.

1. Quinazoline

The anomalous behavior of quinazoline was first discovered by Albert *et al.*³⁵ who made the surprising observation that 4-methylquinazoline (pK_a 2.5) was a weaker base than quinazoline (pK_a 3.5). Mason³⁶ then observed that the ultraviolet spectrum of the quinazoline cation was abnormal but that the spectrum of 4-methylquinazoline was normal (see Fig. 2). These anomalies led to the suggestion that water adds covalently to the cation of quinazoline^{36, 37} to give **12** ($R = H$). The occurrence and position of hydration were confirmed¹² by a detailed study of the ultraviolet and infrared spectra of the anhydrous and hydrated hydrochlorides and by mild oxidation of the cation to 4(3*H*)-quinazolinone. Using the rapid-reaction technique (the continuous-flow method), the spectrum of the unstable



neutral species **13** ($R = H$) was obtained; the stopped-flow method enabled the pK_a^y value for **13** ($R = H$) to be determined as 7.77,¹⁹ which is in agreement with the value of 7.64 for the N-methyl derivative (**13**; $R = Me$). The structure of **13** ($R = H$) was arrived at from the similarity of its spectra (in water and cyclohexane) to that of its methyl derivative (**13**; $R = Me$), which has a well-established structure.³⁸ The possibility of ring-chain tautomerism in **13** ($R = Me$) was excluded because the infrared spectrum (solid and solution) did not show a band corresponding to the carbonyl stretching frequency.¹⁹ The similarity of the spectra and of the spectral changes on protonation of both **13** ($R = H$) and **13** ($R = Me$) led to assignment of the correct structure (**12**; $R = H$) to the hydrated cation of quinazoline.

2. Substituted Quinazolines

The neutral species of substituted quinazolines are predominantly anhydrous. The ratio of the hydrated to the anhydrous neutral species

³⁵ A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.* 3832 (1954).

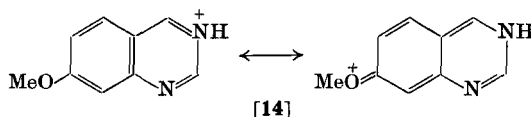
³⁶ A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.* 4191 (1956).

³⁷ A. Albert, *Chem. Soc. (London) Spec. Publ. No. 3*, 138 (1955).

³⁸ D. J. Fry, J. D. Kendall, and A. J. Morgan, *J. Chem. Soc.* 5062 (1960).

of quinazoline¹⁴ is 5.5×10^{-5} (determined as described in the following review¹⁰), but the derivatives have somewhat different values depending on the position and nature of the substituent. For 5-, 6-, 7-, and 8-nitroquinazolines¹⁴ this ratio is 2.1×10^{-3} , 1.5×10^{-3} , 0.8×10^{-3} , and 10×10^{-3} , respectively, indicating the electron-attracting property of the nitro group. 2-Hydroxyquinazoline is hydrated to the extent of about 25% in the neutral species.²³

The cations of quinazolines that have a strong $-I$ substituent (e.g. Cl, NO₂) are almost completely hydrated, and those with a weaker $-I$, or with a $+I$, substituent (e.g. OMe, OH, NH₂, Me) may contain a small proportion (about 10–25%) of the anhydrous cation.¹³ Two important exceptions are now discussed. Substituents in the 4-position, whether $-I$ or $+I$, have a strong dehydrating effect (cf. Section II, C). Again, when a strongly tautomeric ($+T$) substituent (sometimes called a mesomeric substituent) is placed *para* (i.e. in position 7) to the carbon atom C-4, the tendency to hydrate is strongly reduced. This example of "action at a distance" was demonstrated in 7-methoxy-, 7-hydroxy, and 7-amino-quinazoline.¹³ The tautomeric effect, which is absent or barely perceptible in the 5-, 6-, and 8- (but present in the



7-) isomers is due to the strong contribution to the cation by resonance-stabilized forms like **14**. The electron enrichment of C-4 (by delocalization of the positive charge on N-3) repels the negatively charged end of the water molecule as it approaches the 4-position during hydroxylation.

Most substituents (Cl, Me, OMe) in the 2-position have only a small effect, if any, on the hydration of the quinazoline cation; they are similar in this respect to substituents in the 5-, 6-, and 8-positions (see above). Although hydration in the 2-aminoquinazoline cation was at first considered absent,¹³ a closer examination of the entire spectra of both species indicated that the cation spectrum may be that of a mixture. Hydration in the cation has now been confirmed by the rapid-reaction technique (the stopped-flow method) which showed that the unstable hydrated neutral species had a half-life of 4.0 sec at 20° and pH 9.60.³⁹ The 2-hydroxyquinazoline cation has not been studied, but

³⁹ W. L. F. Armarego, unpublished results (1963).

the spectral differences²³ between the neutral species and the cation are not unlike those of 2-aminoquinazoline. The cations of 2-mercaptoquinazoline (which exists mainly in the thione form just as 2-hydroxyquinazoline exists mainly in the oxo form) and 2-methylmercaptoquinazoline are partly hydrated.⁴⁰

In examples where the hydrated cations contain between 10–80% of the anhydrous species, ultraviolet spectra corresponding to mixtures were obtained. It was possible in these cases, by carrying out rapid reactions on the neutral molecule and recording the extinctions at suitable wavelengths, to estimate the amount of hydrated species in the cation (see Table V in ref. 10).¹³

The anions of 2-, 5-, 6-, 7-, and 8-hydroxyquinazoline are anhydrous.¹³

The cation of 4,4'-biquinazolinyl and its 2,2'-dimethyl derivative readily add water across the 3,4- and 3',4'-double bonds, but the cation of 2,2'-biquinazolinyl is not hydrated. Hydration in the 4,4'-isomers has been attributed to restricted rotation about the 4,4'-bond, a steric effect which is relieved by hydration. The ultraviolet spectrum of 2,2'-biquinazolinyl (neutral species and cation) shows that there is considerable conjugation between the quinazoline groups. Covalent hydration is absent from the latter compound because it would otherwise destroy the extended conjugation present.

3. Quinazoline 3-Oxides

Quinazoline 3-oxide is similar to quinazoline in its mode of hydration.^{16,34} The neutral species of the parent substance and all the derivatives so far examined are predominantly anhydrous. The cations, however, were seen to be hydrated from anomalies in the ultraviolet spectra and the ionization constants; e.g., quinazoline 3-oxide and its 4-methyl derivative have pK_a values of 1.47 and 0.06, respectively. The structure of the quinazoline 3-oxide cation (**12**; R = OH) was deduced from spectral comparisons with suitable quinazolines and by gentle oxidation to the corresponding 4-oxo compound.¹⁶ In the cation of each substituted quinazoline 3-oxide, the hydration pattern with chloro, methyl, and methoxy groups substituted in the benzene ring was the same as in the corresponding substituted quinazolines. A methyl group in the 4-position was highly effective in minimizing hydration in the cation. Most of the conclusions were arrived at by examination of the spectral changes, in dilute and concentrated acid (see Section II, B), of the N-oxides with and without a 4-methyl group.¹⁶ It is of interest to note the close resemblance between quinazoline and quinazoline 3-oxide cations, although the

⁴⁰ A. Albert and G. B. Barlin, *J. Chem. Soc.* 3129 (1962).

^{40a} W. L. F. Armarego and R. E. Willette, *J. Chem. Soc.*, in press.

higher acidities which are necessary (because of the lower pK_a values) to protonate the N-oxide molecules have a dehydrating effect. The rapid-reaction technique was found unsuitable for weak bases of this type (see Section II, E).¹⁶

D. TRIAZANAPHTHALENES

1. 1,3,*x*-Triazanaphthalenes

These compounds are discussed in two separate groups: (a) the 1,2,3- and 1,2,4-triazanaphthalenes, and (b) the 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-triazanaphthalenes.

(a) 1,2,3-Triazanaphthalene has not been prepared but several observations⁴¹ suggest that it would behave as an unstable diazonium compound. The neutral species of the 3-oxide was stable at pH 7.1, although it decomposed readily in acid solution. The neutral species was considered to be anhydrous because the spectrum at pH 7.1 resembled that of 4-methyl-1,2,3-triazanaphthalene 3-oxide, in which hydration would be minimized by the "blocking effect" of the methyl group.¹⁴ Decomposition in acid most probably involves addition of water across C-4 and N-3 because *o*-azidobenzaldehyde was formed. The 4-methyl derivative underwent similar decomposition.

The ultraviolet spectra of the neutral species and the cation of 1,2,4-triazanaphthalene are very similar, and the prediction that hydration would not occur is confirmed also by the pK_a value of -0.8 .¹⁴

(b) 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-Triazanaphthalenes have been studied in detail, and their neutral species were shown to be predominantly anhydrous. The ratios of the hydrated to the anhydrous forms in 1,3,5-, 1,3,7-, and 1,3,8-triazanaphthalene were 0.45×10^{-2} , 2.3×10^{-2} , and 0.20×10^{-2} , respectively. Neither this ratio nor the pK_a value for 1,3,6-triazanaphthalene could be measured because the compound decomposed rapidly in acid solution. The neutral species also, at pH 7.1, showed small changes in the spectrum after 3.5 hr (at 20°), and after 2 weeks at this pH the substance was completely converted into 4-aminopyridine-3-aldehyde.¹⁴ The other three triazanaphthalenes were very stable under the same conditions, but they decomposed rapidly in *N*-sodium hydroxide.

The spectra of 1,3,5-, 1,3,7-, and 1,3,8-triazanaphthalene cations revealed that they were predominantly hydrated, and mild oxidation to the corresponding 4-oxo compounds indicated that hydroxylation took place on C-4. Ring-chain tautomerism in the cation was excluded,¹⁴ at least during the first 45 min after mixing, because negative aldehyde tests²¹ were obtained with *p*-nitrophenylhydrazine. 1,3,6-Triazanaphthalene, under the same conditions, gave a yellow precipit-

⁴¹ J. G. Erickson, P. F. Wiley, and V. P. Wystrach, "The, 1,2,3- and 1,2,4-Triazines, Tetrazines, and Pentazines." Wiley, New York, 1956.

ate of the hydrazone after 3 min. Protonation of the 1,3,5-, 1,3,7-, and 1,3,8-isomers was thought to occur in the pyrimidine ring because the pK_a^y values (ionization of hydrated species) were similar for all three isomers.¹⁴

As in the neutral species (above), hydration in the cations of 1,3,5-, 1,3,7-, and 1,3,8-triazanaphthalenes is followed by slow ring-opening, but the amount of ring-opened product is negligibly small in the first 30 min, allowing enough time for accurate determination of the ionization and rate constants. The ring-opening reaction, however, appears to be irreversible, because it is followed by a more rapid degradation to the corresponding aminopyridinealdehydes.¹⁴

These triazanaphthalenes and the *Bz*-nitroquinazolines are good examples to demonstrate the fact that pK_a^{eq} values are unsuitable for comparative purposes. Thus, in Table II, comparison of the pK_a^{eq} values suggests that the seven negatively substituted quinazolines are stronger bases than quinazoline, which is absurd in view of the well-known base-weakening effect of the nitro group and an extra ring-nitrogen atom. The pK_a^y values, however, which refer to the hydrated neutral species and their cations are in the correct order.

TABLE II
COMPARISON OF pK_a^{eq} AND pK_a^y VALUES OF
QUINAZOLINE AND SOME DERIVATIVES¹⁴

Compound	pK_a^{eq}	pK_a^y
Quinazoline	3.51	7.77
5-Nitroquinazoline	3.75	6.43
6-Nitroquinazoline	4.18	7.02
7-Nitroquinazoline	4.05	6.15
8-Nitroquinazoline	4.00	6.00
1,3,5-Triazanaphthalene	4.11	6.46
1,3,7-Triazanaphthalene	4.70	6.35
1,3,8-Triazanaphthalene	3.85	6.56

In 2-hydroxy-1,3,8-triazanaphthalene (the only 1,3,x-triazanaphthalene with an acidic function that has been studied) the percentage of the hydrated species in the neutral molecule and in the anion was found^{27a} to be 90 and 6, respectively.

2. 1,4,x-Triazanaphthalenes

1,4,6-Triazanaphthalene, although at one time thought to undergo ring-opening under acidic conditions, is now known to form a stable hydrated cation.^{25, 27a} Examination of the ultraviolet spectra by the stopped-flow technique has shown that the ratio of the hydrated to the anhydrous forms is 95 and 0.0001 for the cation and neutral molecule, respectively, at equilibrium. This substance hydrates in the 1,2-position. Hydration has also been found in the 3-methyl, 3-hydroxy, and 7-amino derivatives, but not in the 2- or 8-hydroxy derivatives.^{25, 42}

No hydration could be detected in 1,4,5-triazanaphthalene. However, the cation of the 2-hydroxy derivative had been shown to hydrate in the 3,4-position, and the ratio of the hydrated to the anhydrous forms is 16. The hydrate of the neutral species is unstable but has a half-life of 6 min at pH 7, which permits easy measurement of the ionization and rate constants.²⁶

E. TETRAAZANAPHTHALENES

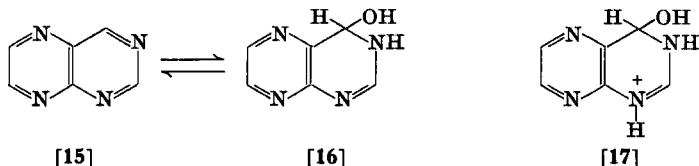
1. Pteridines (1,3,5,8-Tetraazanaphthalenes)

Of all the heteroaromatic compounds that have been examined qualitatively and quantitatively for covalent hydration, the pteridines constitute the largest series. Most of the quantitative relationships which were used in earlier discussions were first derived for the hydroxypteridines.^{27a} Also most of the known examples of hydration in anions were found in this series.

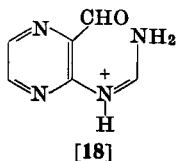
(a) *Pteridine and C-Methyl Derivatives.* The high basic strength of pteridine (pK_a 4.21) was first observed⁴³ in 1951, but the theoretical explanation for it came eleven years later.²⁴ Close examination of the ultraviolet spectra showed that the freshly liberated neutral species altered slowly coming to equilibrium after 10 hr. This change is due to the establishment of the equilibrium $15 \rightleftharpoons 16$, which at 20° is 3.5:1 in favor of **15**. When a solution of pteridine is acidified, the mixture is rapidly converted into the hydrated cation (**17**), which on neutralization is deprotonated to yield a solution consisting predominantly of **16**, but this in turn slowly changes into the original equilibrium mixture of the neutral species. The pK_a value for the protonation of **16** is 4.79. The structure of the hydrated species (**17**) was derived by oxidation

⁴² Y. Inoue and D. D. Perrin, *J. Chem. Soc.* 5166 (1963).

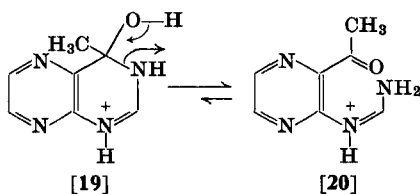
⁴³ A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.* 474 (1951).



to the well-known 4-hydroxypteridine and by the isolation of hydrated salts.²⁴ The spectrum of **17** at pH 2 changed steadily during 2-3 hr, but remained stable thereafter. This change (half-life ~ 35 min) corresponded to the ring-opening reaction $17 \rightleftharpoons 18$. The constitution of **18** was derived by spectral comparison with 2-aminomethyleneamino-3-formylpyrazine oxime and its cation. The pK_a value for **18**, determined by rapid-reaction methods, is 5.17.



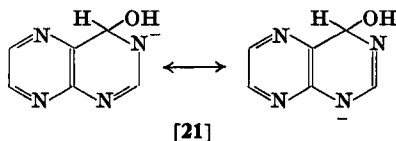
The "blocking effect" of the methyl group in 4-methylpteridine has been found to decrease the ratio of the hydrated to the anhydrous species in the neutral molecule²⁴ and in the cation,⁴⁴ but the small proportion of hydrated cation rapidly undergoes the ring-opening reaction⁴⁴ $19 \rightarrow 20$ and hence is steadily regenerated from its anhydrous form. 2-Methylpteridine behaves like pteridine, but in 7-methylpteridine the "action at a distance" (+*M*) effect of the methyl group (see Section III, C, 2) produced a smaller ratio of the hydrated to anhydrous species.²⁴



In strong alkaline solution pteridine behaves as a weak acid^{24, 45} with a pK_a value of 11.21. To explain this property, the resonance-stabilized anion **21** was derived⁴⁵ from the hydrate **16**.

⁴⁴ Y. Inoue and D. D. Perrin, *J. Chem. Soc.* 2648 (1963).

⁴⁵ A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.* 2066 (1956).



(b) *2-Aminopteridine and Its Methyl Derivatives.* Hydration in the 2-aminopteridine cation was suspected when the yellow color of an aqueous solution disappeared on acidification. Also, the pH readings, on titration with acid and back titration with alkali, traced out a hysteresis loop (cf. Fig. 1). Other examples studied were 2-amino-4-methyl-, 2-amino-6-methyl-, 2-amino-4,6-dimethyl-, 2-amino-4,7-dimethyl-, 2-amino-6,7-dimethyl-, 2-amino-4,6,7-trimethyl-, 2-methyl-amino-, and 2-dimethylamino-pteridine.²¹ Paradoxically, 2-aminopteridine is a stronger base than any of its methyl derivatives, and, moreover, each dimethyl derivative is a weaker base than either of its

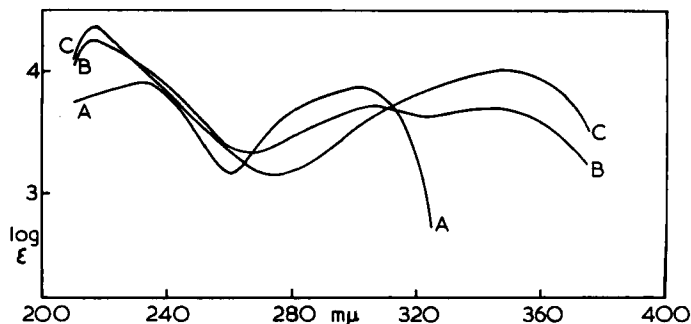


FIG. 5. Ultraviolet spectra of the cations of 2-aminopteridines: (A) unsubstituted, (B) 4-methyl, and (C) 4,7-dimethyl.

parent monomethyl derivatives. The spectra of the neutral species of 2-aminopteridine and all its methyl derivatives resemble one another, which indicates that they are predominantly anhydrous. On the other hand, the cationic spectrum of 2-aminopteridine differs very much from that of the 4-methyl derivative, which is the more normal. This difference indicated that the cations of 2-aminopteridines were hydrated and that this effect was largely repressed by the "blocking effect" of the methyl group in the 4-position. This was clearly shown by a comparison of the cationic spectra in water and in anhydrous dichloroacetic acid. The ratio of the extinction coefficients allowed calculation of the extent of water-addition, which decreased from 99%

to 1% in the order: unsubstituted > 6-Me > N-Me \approx 7-Me > 6,7-Me₂ > 4-Me > 4,6-Me₂ > 4,7-Me₂. These results agree well with the pK_a^{eq} values. Ring-opening was excluded in this series because acidic solutions gave negative aldehyde tests.²¹ Fig. 5 shows how the presence of the methyl group in the 4-position can partially block hydration of the 2-aminopteridine cation. When this "blocking effect" is assisted by the +*M* effect of another methyl group in the 7-position, blocking of hydration becomes complete. The ultraviolet spectra of the neutral species of the three substances shown in Fig. 5 are identical.

(c) *Hydroxypteridines*. The neutral species of 2- and 6-hydroxypteridines form stable covalent hydrates, but the 4- and 7-isomers do not. 2-Hydroxypteridines add water across the C-4 and N-3 bond, whereas 6-hydroxypteridines add water across the C-7 and N-8 bond. The fact and positions of hydration were determined by the anomalous ultraviolet spectral changes between the neutral species and the anion, by comparison of the spectra and ionization constants with those of the corresponding dihydro derivatives (see Table I), and by mild oxidation to the well-known 2,4-dihydroxy- and 6,7-dihydroxypteridines.⁷ Confirmation of the positions of hydration was obtained by use of the "blocking effect" of a methyl group in the 4- and 7-positions, respectively.^{18, 23}

6-Hydroxy- and 6-hydroxy-7-methyl-pteridine cations are so strongly hydrated that the "blocking effect" of the methyl group is not obvious.¹⁸ In the neutral species, on the other hand, 6-hydroxypteridine has a ratio of the hydrated to the anhydrous forms of 125, whereas 6-hydroxy-7-methylpteridine has a ratio of ~ 1 .⁴⁶ By analogy with this, other hydroxypteridines which are hydrated to some extent in the neutral species would be expected to have a still higher proportion of the hydrated species in the cation. However, because of the low basic pK_a values of 2-hydroxypteridine and its derivatives, the acid required for protonation is apparently strong enough to have a dehydrating effect (see Section II, B, 2).

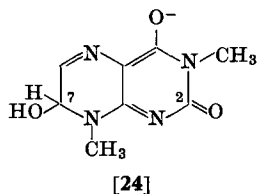
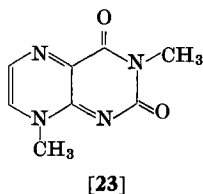
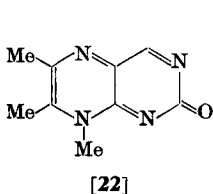
Most of the work done in the pteridine series has been concerned with the equilibria between the neutral species and the anions. This work was more fruitful than that involving the cations because all three of the values, pK_a^x , pK_a^{eq} , and pK_a^y (for definitions, see Section II, A), could be determined, and, from these, ratios of the hydrated to the anhydrous forms were calculated. Furthermore, the kinetics in the

⁴⁶ Y. Inoue and D. D. Perrin, *J. Chem. Soc.* 2600 (1962).

pH region 4–11 were studied accurately, and from the k_{obs} of the hydration–dehydration process, k_h (rate constant for hydration) and k_d (rate constant for dehydration) were derived.¹⁰ The anions were considerably less hydrated than the neutral species.⁴⁶

The ratio, at equilibrium, of the hydrated to anhydrous forms (for both neutral species and anions) has been measured for the following: 2-hydroxypteridine and its 4-, 6-, and 7-methyl and 6,7-dimethyl derivatives; 6-hydroxypteridine and its 2-, 4-, and 7-methyl derivatives; 2,6-dihydroxypteridine; and 2-amino-4,6-dihydroxypteridine.⁴⁶ The following showed no evidence of hydration: 4- and 7-hydroxypteridine; 2,4-, 2,7-, 4,7-, and 6,7-dihydroxypteridine; and 2-amino-4-hydroxypteridine. The kinetics of the reversible hydration of 2-hydroxypteridine and its C-methyl derivatives (also 2-mercaptopteridine) have been measured in the pH region 4–12, and all these reactions were found to be acid-base catalyzed.¹⁰ The amount of the hydrated form in the anions is always smaller than in the neutral species, but it is not always negligible. Thus, the percentages in 2-hydroxy-, 2-hydroxy-6-methyl-, 2-mercapto-, and 2,6-dihydroxypteridine are 12, 9, 19, and 36%,⁴⁶ respectively (see also Table VI in ref. 10).

(d) *N-Methyl-hydroxypterines*. Many pteridines which, in the anhydrous form, lack an ionizable hydrogen atom give stable anions clearly indicating that hydration of the neutral species must precede formation of anions. The various N-alkyl derivatives of 2- and 6-hydroxypteridine behave in this way.



6,7,8-Trimethyl-2-pteridinone (**22**) has acidic properties ($\text{p}K_a$ 10.26) and hence must be hydrated in the anion. The neutral species exhibits a NH-stretching band at 3414 cm^{-1} in chloroform solution and hence must be at least partly hydrated.⁷ The suggestion that the hydroxyl group is attached to C-7 needs to be confirmed. Fidler and Wood prepared several analogues of **22** and noted their affinity for water, which they considered not to be covalently bound in the neutral

species but to be covalently bound in the anion.⁴⁷ The ultraviolet spectra do not reflect such a large constitutional change on ionization, and the subject needs further exploration.

6,7,8-Trimethyl-4-pteridinone is an acid of pK_a 9.5 and is therefore hydrated in the anion.⁷ The hydroxyl group is thought to be attached to C-7 and the negative charge to resonate between N-1 and N-3. The neutral species cannot be appreciably hydrated because its ultraviolet spectrum is very different from that of the anion.

Other anion-forming substances in which hydration has been established include 1- and 3-methyl-2-pteridinone, 3,6,7-trimethyl-2-pteridinone,⁷ and 5-methyl-6-pteridinone.⁴⁵

Although 2,4-dihydroxypteridine gives no signs of a tendency to hydrate, the 3,8-dimethyl derivative **23** (3,8-dimethyl-2,4-pteridinone) has a pK_a of 10.4 and, hence, presumably, is hydrated. The anion absorbs (λ_{max}) at 306 $m\mu$ and the neutral species at 393 $m\mu$, figures which indicate that a large structural change occurs in passing from one species to the other.⁴⁸ This is one of the few known examples where an anion is more hydrated than the corresponding neutral species,⁴⁹ because the ionizable hydrogen is derived from the water molecule that has been added. The anion appears to be stabilized by resonance between the form **24** and that with the negative charge on O-2. The 8-methyl derivative (4-hydroxy-8-methyl-2-pteridinone) has an anion which exhibits peaks⁴⁸ at both 307 and 405 $m\mu$, suggesting that it is a mixture of the hydrated (principally) and anhydrous forms,⁴⁹ although prototropy between N-1 and N-3 must also be taken into consideration.

There are indications^{50, 51} that bulky groups in the 7- or 8-position decrease the absorption in the 405 $m\mu$ region (and hence they can presumably increase hydration in the anion, a somewhat surprising result).

4-Hydroxy-8-hydroxyethyl-6,7-dimethyl-2-pteridinone has been shown to have the same absorption spectrum in alkaline solution as its 1,7-dihydro derivative, namely peaks at 231, 283, and 316 $m\mu$. This

⁴⁷ W. E. Fidler and H. C. S. Wood, *J. Chem. Soc.* 3980 (1957).

⁴⁸ Dr. W. Pfeleiderer (Stuttgart), personal communication (1962).

⁴⁹ P. Hemmerich, in "Pteridine Chemistry" (W. Pfeleiderer and E. C. Taylor, eds.), p. 143. Pergamon Press, Oxford, 1964.

⁵⁰ W. Pfeleiderer and G. Nubel, *Chem. Ber.* **93**, 1406 (1960).

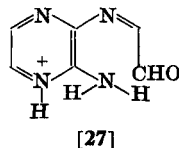
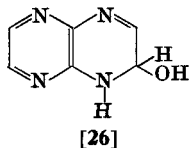
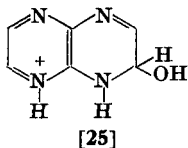
⁵¹ C. H. Winestock and G. W. E. Plaut, *J. Org. Chem.* **26**, 4456 (1961); G. F. Maley and G. W. E. Plaut, *J. Biol. Chem.* **234**, 641 (1959).

observation has been interpreted to mean that the anion is completely hydrated while the neutral species is anhydrous.⁵² This substance is a model of the pteridine intermediate in the biosynthesis of riboflavin, and many analogues are known.^{50, 51}

(e) *Chloro- and Mercapto-pteridines*. (See Note Added in Proof, page 41.)

2. *Pyrazinopyrazines (1,4,5,8-Tetraazanaphthalenes)*

1,4,5,8-Tetraazanaphthalene has a pK_a value of 2.51. This differs greatly from the calculated value (-2.7)^{52a} and, because the system (during the potentiometric measurements) took some time to come to equilibrium, hydration in the cation was suspected. Further evidence came from the observation that the fine structure which is observed in the ultraviolet spectrum of the neutral species in water and cyclohexane is absent from the spectrum determined in aqueous acid. Protonation of the compound caused the long-wavelength band to shift $20\text{ m}\mu$ towards the visible (see Fig. 3). After rapid neutralization of an acid solution the spectrum measured was that of the hydrated neutral species, which dehydrated very slowly to the anhydrous neutral species. The dehydration at pH 8.1 was not complete until 16 days had elapsed: this is one of the most stable hydrated neutral species yet encountered in any series.¹⁵ Structure **25** was assigned to the hydrated cation and **26** to the corresponding neutral species. Ring-opening to give **27** was excluded on the grounds of a negative test for aldehydes (see Section V) and also by mild oxidation to 2,3-dihydroxy-1,4,5,8-tetraazanaphthalene, which had an identical infrared spectrum with an authentic sample. Further support for the hydrated structure was obtained from the spectrum in anhydrous dichloroacetic acid, which must be that of the anhydrous neutral species (because the pK for the anhydrous form is -2.7), and addition of water restored the spectrum of the hydrated cation.¹⁵



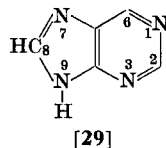
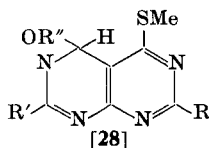
⁵² T. Rowan, H. C. S. Wood, and P. Hemmerich, *Proc. Chem. Soc.* 260 (1961).

^{52a} Calculated by subtracting 2.7 (due to the base-weakening effect produced by removal of four methyl groups) from the pK_a (-0.02) of 2,3,6,7-tetramethyl-1,4,5,8-tetraazanaphthalene, which forms an anhydrous cation.¹⁵

Similar analyses of 2-methyl-, 2,3-dimethyl-, 2,3,6-trimethyl-, and 2,3,6,7-tetramethyl-1,4,5,8-tetraazanaphthalene showed that all the neutral species were anhydrous. Whereas the cations (in aqueous solution) of the 2-methyl and 2,3-dimethyl derivatives were predominantly ($> 95\%$) hydrated, the 2,3,6-trimethyl cation had only a trace of hydrated species and that of the 2,3,6,7-tetramethyl derivative was anhydrous.¹⁵

3. Other Tetraazanaphthalenes

The hydrochlorides of several 1,3,6,8-tetraazanaphthalenes have been shown by n.m.r. studies to have water or methanol bound across the 5,6-bond.⁵³ The affected substances are **28** ($R = \text{Me}$, $R' = R'' = \text{H}$), **28** ($R = R' = R'' = \text{H}$), **28** ($R = R' = \text{H}$, $R'' = \text{Me}$), and **28** ($R = R' = R'' = \text{Me}$). These hydrates readily undergo acid hydrolysis to give (substituted) 4-formamidopyrimidine-5-aldehyde.



F. PURINES AND AZAPURINES

For reasons discussed in Section VI, a survey of the purine series (**29**) is being made in this Department, but so far no example (including 2-hydroxy- and 8-trifluoromethyl-2-hydroxy-purine) of covalent hydration has come to light. An examination of ionization constants⁵⁴⁻⁵⁶ disclosed no apparent anomalies, although the interpretation is made more difficult by the ease of anion formation in the 9-position, which often competes with that from other anionic substituents. The only abnormal spectrum⁵⁵⁻⁵⁷ seems to be that of the anion of 2-mercaptopurine which is being further examined.

This does not exclude the possibility that hydration occurs too rapidly to be detected with existing apparatus. Special point is given to this conclusion by a recent survey of 8-azapurines.⁵⁸ The abnormal

⁵³ W. A. Ehrhart, Ph.D. Thesis, Princeton University, 1963; personal communication from Prof. E. C. Taylor (1963).

⁵⁴ A. Albert and D. J. Brown, *J. Chem. Soc.* 2060 (1954).

⁵⁵ D. J. Brown and S. F. Mason, *J. Chem. Soc.* 682 (1957).

⁵⁶ G. B. Elion, *J. Org. Chem.* **27**, 2478 (1962).

⁵⁷ S. F. Mason, *J. Chem. Soc.* 2071 (1954).

⁵⁸ A. Albert and D. D. Perrin, unpublished results (1963).

ultraviolet spectrum and pK_a value indicated that the 8-azapurine cation is hydrated. Ready oxidation with acidified hydrogen peroxide to 6-hydroxy-8-azapurine proved that the 1,6-double bond in 8-azapurine is the site of hydration.

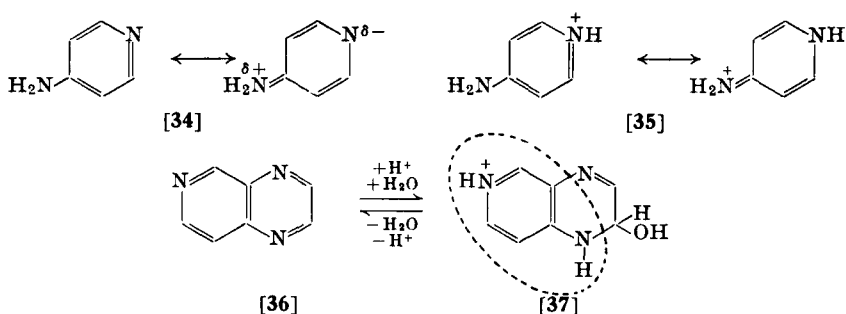
2-Hydroxy-8-azapurine was shown by rapid-reaction techniques (see Section II, E) to be anhydrous in the anion and hydrated in the neutral species. The hydration reaction has a half-time of about 0.5 second, which is too rapid for exact measurements with existing apparatus. The cation of 2-amino-8-azapurine was shown to have an anomalous pK_a value and ultraviolet spectrum, although its 6-methyl derivative is quite normal. Hydration in this case proved to be too fast to register in the rapid-reaction apparatus.⁵⁸

IV. Factors in the Stabilization of Covalent Hydrates

It is easy to understand why an aldehyde, or even a heteroethylenic substance, should hydrate readily. If a double bond is highly polarized, it is certain to attract a water molecule (or one of the two water ions) to within reacting distance. However, it is not at once evident why an apparently fully aromatic molecule like pteridine should react so readily with water. The answer to this problem is to be found in the high electron-affinity of a nitrogen atom when it is doubly bonded. Such an atom has the electron-withdrawing force of a nitro group. Thus, the presence of several doubly bonded nitrogen atoms in one aromatic ring (especially if they are placed *meta* to one another so that the separate effects are entirely additive) depletes the π -electron layer so strongly that normal aromatic stability is destroyed. As a result, an isolated and highly polarized double bond is exposed, and reactions occur that are typical of such a bond. Thus, many nucleophilic reagents are easily added to the 3,4-double bond of 2-hydroxypteridine²³ and to the 7,8-double bond of 6-hydroxypteridine.¹⁸ Such reagents include ammonia, hydroxylamine, methanol, and the Michael reagents (such as ethyl cyanoacetate, and even acetone) (cf. Section III, A). Also, a second molecule of the hydroxypteridine can be added to give a dimer.⁶

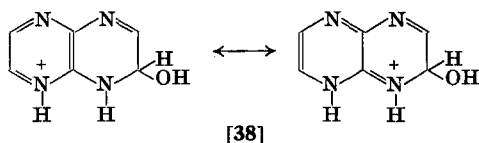
However, water is a much weaker nucleophilic reagent than most of the above substances and therefore would not remain strongly bound unless some further forces were operative. It is our belief that resonance is the principal cause of this extra stabilization. We have found that these resonances are varied in nature, but they all fit into one or the other of the following principal classes.

⁵⁹ G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry." Prentice-Hall, London and New York, 1944.



5.2 for pyridine) to this difference in resonance.⁶⁰ The 4-aminopyridine-type resonance is actually a vinylogous amidine resonance, and its stability depends upon the similarity in energy of such *para*-quinonoidal conjugations and the Kekulé-type (or benzenoid) conjugations. The simplest compound so far discovered^{25, 27a} that shows this resonance is 1,4,6-triazanaphthalene (36), which is predominantly anhydrous in the neutral species but forms a highly hydrated cation, the 4-aminopyridine component of which is apparent in formula 37. Many of its derivatives behave similarly.²⁵ Examples of stabilization by this type of resonance have been much studied in the 6-hydroxypteridine series.^{18, 22}

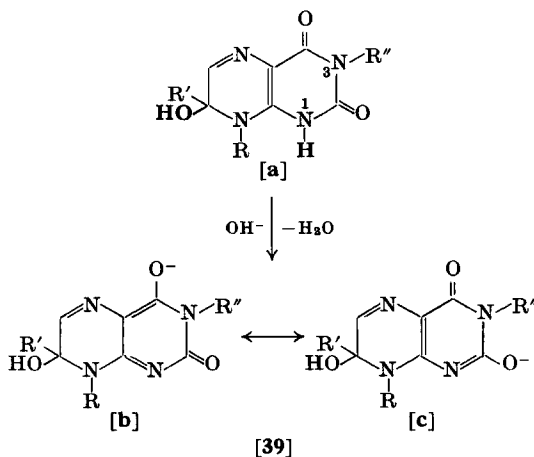
5. 2-Aminopyridine and 2-aminopyrazine-type resonances. The *ortho*-quinonoid resonance in 2-aminopyridine, corresponding to the *para*-quinonoid resonance in 4-aminopyridine (34 and 35), is much weaker and, for the present purposes, of borderline significance. Thus, although 1,4,5-triazanaphthalene is anhydrous, a 2-aminopyridine-type of hydration stabilization has been found in the cation of its 2-hydroxy derivative.²⁶ However, when a further ring-nitrogen atom was introduced into the pyridine ring of 1,4,5-triazanaphthalene to give 1,4,5,8-tetraazanaphthalene, it was found that the hydrated cation was readily formed and also that the hydrated neutral species was relatively stable.¹⁵ The cause of this stabilization is the 2-aminopyrazine-type resonance as shown in the cation 38. The extent to



⁶⁰ A. Albert, R. J. Goldacre, and J. N. Phillips, *J. Chem. Soc.* 2240 (1948).

which 2-aminopyrazine resonance is stronger than 2-aminopyridine resonance can perhaps be judged by the difference in the pK values between these 2-amino derivatives and the parent substances, *viz.* 2.5 and 1.6, respectively.

6. *Oxygen anion resonance.* This means of stabilizing hydration depends on the resonance shown in **39b-c**, which is akin to *2,4-dihydroxypyridine anion resonance*. An example of its occurrence (e.g. **24**) is mentioned in Section III, E, 1, d. This resonance bears a close resemblance to the pteridine anion resonance shown in formula **21**,

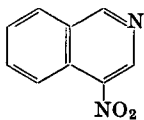


where the addition of water to pteridine produces a system which is capable, in alkaline solution, of losing a proton from a nitrogen atom to form the anion **21**. In contrast, the resonance now being discussed involves the loss of a proton from N-1 in **39a** to produce an anion which is tautomeric with **39b** and **39c**.

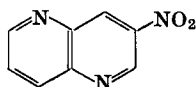
In all the examples studied, the difference in the free energy between the anhydrous and hydrated species is 4 kcal/mole or less.¹⁰ Both electron deficiency and resonance stabilization are necessary for covalent hydration to be measurable.²⁰ The necessity for electron deficiency is clearly shown in the following examples. The cation of 1,4,5-triazanaphthalene²⁶ is anhydrous, but the cation of 1,4,5,8-tetraazanaphthalene is predominantly hydrated.¹⁵ 1,6-Naphthyridine cation is anhydrous, whereas the cations of the 3- and 8-nitro derivatives are predominantly hydrated.²⁰ Also, the percentages of the hydrated form in the neutral species of 2-hydroxy-1,3-diaza-, 1,3,8-

triazaz-, and 1,3,5,8-tetraazanaphthalene are 25, 90, and 99.7%, respectively.^{23,42} Again, the ratios of the hydrated to anhydrous forms in the neutral species of 1,3-diaza-, 1,3,8-triaza-, and 1,3,5,8-tetraazanaphthalene are 5.5×10^{-5} , 2.0×10^{-3} , and 2.9×10^{-1} , respectively.^{14, 42}

That resonance stabilization is just as essential as electron deficiency is shown by the anhydrous nature of both the neutral species and the cation²⁰ of 4-nitroisoquinoline (**40**) and 3-nitro-1,5-naphthyridine (**41**), for which hydration can cause no extra stabilization by resonance. These two substances are to be contrasted with equally electron-deficient substances which form strongly resonant hydrates, *viz.* quinazoline¹² and 1,3,5-triazanaphthalene,¹⁴ respectively. No hydration could be detected in phthalazine or 8-methyl-1,6,7-triazanaphthalene (a 5-azaphthalazine).⁶¹

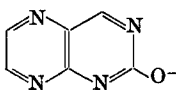


[40]

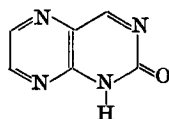


[41]

In general, electron-releasing groups (e.g. —NH_2 , —OH) diminish or prevent covalent hydration by decreasing the electron deficiency in the nucleus. This diminution becomes ineffective if a new kind of stabilizing resonance is facilitated by the substituent, e.g. the urea-type resonance and the 4-aminopyridine-type resonance in 2- and 6-hydroxypteridine, respectively. The reluctance of the anions of these substances to form hydrates is attributed to the stable benzenoid system, e.g. **42**, in the anhydrous anion compared with the predominantly lactam form of the neutral species, e.g. **43**.



[42]



[43]

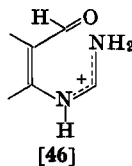
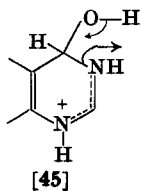
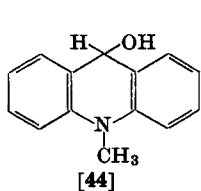
Thus far, this section has been concerned with the explanation of the factors responsible for the covalent hydration of heteroaromatic substances. Heteroethylenic substances (e.g. the dihydropyridines,

⁶¹ W. L. F. Armarego, *J. Chem. Soc.* 6073 (1963).

dihydropyrans, and dihydropyrroles) add water much more readily, but this behavior is far less remarkable.

This section may be appropriately concluded with a comparison between two phenomena: (a) covalent hydration and (b) the pseudobase formation that occurs when alkali is added to an aqueous solution of a quaternary heterocycle.⁶² The similarity between these two processes resides in the conversion of an aromatic ring into a nonaromatic ring bearing a secondary alcohol group. However, the conditions for the production of this change are usually very different. Thus acridine methochloride, which is not hydrated, gives the pseudobase **44** with alkali, whereas 2-aminopteridine hydrochloride, which is completely hydrated, gives anhydrous 2-aminopteridine with alkali. Some of this difference is due to the greater ease with which the N—H bond is broken (with loss of water) in hydrated 2-aminopteridine, as compared to the N—CH₃ bond (with loss of methanol) in the acridine pseudobase.

In those few cases where hydration and pseudobase formation parallel each other, the agreement can be traced to the fortuitous circumstance that the structure and electronic configuration of the molecule permit both phenomena to occur simultaneously. Quinazoline-3-methochloride, one of these rare examples, is discussed in Section III, C, 1.



V. Ring-Opening

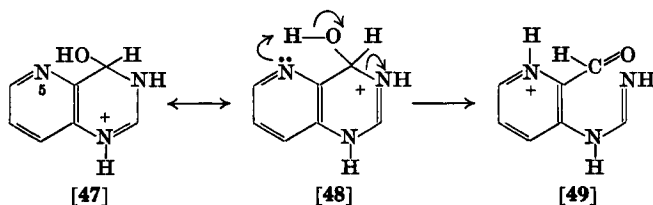
The above account of resonance stabilization explains why so many azanaphthalenes become strongly hydrated, and it may also help to explain why the hydrated forms are usually stable against rupture of the C—N bond by acid. It is true that ring-opening necessitates only simple prototropic rearrangement (**45** → **46**) and that the product obviously retains some of the stabilizing resonance. However, if, as seems likely, the resonance of the hydrates also includes hybridization with the adjacent ring system, then these cyclic hydrates are further stabilized by co-planarity with the aromatic ring. In a non-cyclic

⁶² D. Beke, *Advan. Heterocyclic Chem.* **1**, 167 (1963).

structure (46), co-planarity is more difficult to achieve. Experimentally, ring-opening is demonstrated by establishing the presence of the functional groups which are expected to be formed.⁸ The commonest of these is the aldehyde group, and *p*-nitrophenylhydrazine is the most suitable reagent because of the pH range within which it can form hydrazones.²¹ Thus a 0.03*M* solution of the substance to be tested is made in glycine or citrate buffer at any desired pH between 0.4 and 3.8 and set aside for the desired period. It is then mixed with an equal volume of 0.05*M* *p*-nitrophenylhydrazine made in a buffer of the same pH. If an aldehyde group is present, the color should intensify and/or deepen at once, and a distinct precipitate usually forms within a few minutes²¹; several applications of this method have been reported.^{14, 15} Benzidine has also been used as a test reagent,²⁴ although the pH range in which it is effective is not wide. The kinetics for the reversible ring-opening of pteridine and its C-methyl derivatives have been studied in detail.⁴⁴

The electronic effects (δ^+ on carbon and δ^- on nitrogen) that favor the hydration of heteroaromatic molecules and of Schiff bases to give Dimroth bases are the same as those that would favor the ring-opening of the hydrated heteroaromatic molecules and cleavage of the C—N bond in Dimroth compounds.

Cations are more subject to ring-opening than are neutral species or anions. Thus ring-opening (slow) has been observed in the cations but not in the neutral species of 1,3,5-, 1,3,7-, and 1,3,8-triazanaphthalene at 20°; it is followed by further degradation.¹⁴ 1,3,6-Triazanaphthalene decomposes much faster than its isomers in acidic solution, but follows the usual sequence, 47 → 49.



Ring-closure, e.g. 49 → 48, is favored by any factor which places a positive charge on the aldehydic carbon atom and a negative charge on (or removes a positive charge from) N-3 (and hence on N-1 with which N-3 shares the charge). In 1,3,6-triazanaphthalene, ring-opening is favored¹⁴ because of the high proportion of the positive charge which

resides on N-1 (and/or N-3) in accord with the well-known 4-aminopyridine cation resonance.⁶⁰

The neutral species of 1,3,6-triazanaphthalene, unlike those of its isomers, decomposes at pH 7.1 to give 4-aminopyridine-3-aldehyde, on standing at 20°. The nitrogen atom in position 5 of pteridine must confer extra stability on the hydrated cation, because 1,3,8-triazanaphthalene (from which it is derived by replacing C-5 by a nitrogen atom) is more easily ring-opened by cold acid.

VI. Covalent Hydration in Chemistry and Biology

An understanding of covalent hydration is essential for all who work with heteroaromatic compounds containing doubly bonded nitrogen atoms. As chemists become more aware of the circumstances in which hydration occurs, and the means for detecting it, many new examples will probably be discovered and many puzzling discrepancies solved. Many of the values for ionization constants and ultraviolet spectra which are in the literature refer to partly hydrated equilibrium mixtures and should be replaced by values for the pure substances.

At the present time, the greatest importance of covalent hydration in biology seems to lie in the direction of understanding the action of enzymes. In this connection, the enzyme known as xanthine oxidase has been extensively investigated.^{63, 64} This enzyme catalyzes the oxidation of aldehydes to acids, purines to hydroxypurines, and pteridines to hydroxypteridines. The only structural feature which these three substituents have in common is a secondary alcoholic group present in the covalently hydrated forms. Therefore it was logical to conceive of this group as the point of attack by the enzyme.

A hypothesis for the oxidation of purines in the presence of this enzyme has been elaborated by Bergmann and his colleagues.⁶⁴ It postulates that the purine, often in one of its less prevalent tautomeric forms, is adsorbed on the protein, or the riboflavin coenzyme, of the enzyme; then hydration occurs under the influence of the electronic field of the enzyme, and this must involve a group that is not sterically blocked by the enzyme but which is accessible to the electron-transport pathway of the riboflavin moiety. Finally, the secondary alcohol is assumed to be dehydrogenated in this pathway to give a doubly

⁶³ F. Bergmann and H. Kweitny, *Biochim. Biophys. Acta* **33**, 29 (1959).

⁶⁴ F. Bergmann, H. Kweitny, G. Levin, and D. J. Brown, *J. Am. Chem. Soc.* **82**, 598 (1960).

bonded oxygen atom. The established facts are that purine and all mono- and di-hydroxypurines are oxidized stepwise, through isolable intermediates, to uric acid (2,6,8-trihydroxypurine), and the reduced riboflavin moiety is reoxidized with the aid of the molybdenum and iron present in the enzyme.

The situation in the pteridine series is somewhat more complex.^{64,65} Pteridine, 2-, 4-, and 7-hydroxypteridine, and some of the dihydroxypteridines are oxidized, stepwise and quantitatively, in the presence of xanthine oxidase to a single substance, 2,4,7-trihydroxypteridine. Notably, 6-hydroxypteridine, which readily forms a covalent hydrate, is not attacked.

Bergmann has suggested that oxidation is ruled out at positions (where hydration occurs readily) which are not accessible to the enzyme after the pteridine is adsorbed on it. Alternatively,⁴⁶ the destruction of co-planarity by hydration may prevent adsorption of the pteridine on the enzyme. The case of xanthopterin (2-amino-4,6-dihydroxypteridine) may be relevant. The neutral species of this substance exists as an equilibrium mixture of approximately equal parts of the anhydrous and 7,8-hydrated forms (in neutral aqueous solution at 20°).⁴⁶ Xanthine oxidase catalyzes the oxidation of the anhydrous form in the 7-position but leaves the hydrated form unaffected and about two hours is required to re-establish the former equilibrium.

It seems reasonable to predict that many aspects of covalent hydration will interest the biologist and help him in his work. Many substances with six-membered nitrogen-containing heteroaromatic rings, i.e. the families which are so prone to covalent hydration, are biologically active substances, both natural and artificial. The distribution of substances between water and lipids, a subject of considerable importance to those who study permeability phenomena, is greatly impeded by each water-attracting group present, and the extra hydroxyl group furnished by covalent hydration must be taken into account in investigations of this nature.

Note Added in Proof (p. 31):

(e) *Chloro- and Mercapto-pteridines*. At equilibrium the neutral species of 6- and 7-chloro- and 6,7-dichloro-pteridine are hydrated across the 3,4-double bond to the extent of 31, 30, and 36%, respectively (compare pteridine²⁴ 22%). In acid solution their cations are

⁶⁵ H. S. Forrest, E. W. Hanly, and J. M. Lagowski, *Biochim. Biophys. Acta* **50**, 596 (1961).

almost completely hydrated but undergo ring-opening followed by degradation to the corresponding 2-amino-chloropyrazine-3-aldehydes. Hydrolysis of the chlorine atom in the chloropteridine occurs concurrently with hydration in acid solution and makes measurement of the kinetics more complicated (see ref. 10). In alkaline solution, where anhydrous neutral species are predominant, rapid hydrolysis of the halogen substituent is the major reaction.⁶⁶

An understanding of the reactions between 6-chloropteridine and reagents that can add across a —C=N— bond, i.e. H_2O , PhCH_2SH , and NH_3 , made it possible to find conditions for the preparation of 6-mercaptopteridine. The latter, like 6-hydroxypteridine, is hydrated across the 7,8-double bond of the neutral species and cation.⁶⁷ 6-Methylmercaptopteridine, however, is decomposed (liberates methyl mercaptan) by dilute acid.

⁶⁶ A. Albert and J. Clark, *J. Chem. Soc.*, 1666 (1964).

⁶⁷ J. Clark, personal communication (1964).

Covalent Hydration in Nitrogen Heteroaromatic Compounds: II. Quantitative Aspects

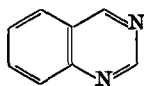
D. D. PERRIN

*Department of Medical Chemistry, Institute of Advanced Studies,
The Australian National University, Canberra, Australia*

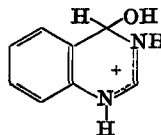
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I. Introduction

Reversible covalent hydration across C=N bonds occurs in a number of nitrogen-containing heterocycles, including pteridine and its 2- and 6-hydroxy derivatives, quinazoline (as the cation), and 1,4,6-triazanaphthalene (as the cation).¹ Among bases giving this reaction, the neutral molecule exists predominantly as the anhydrous form, whereas the cation contains an increased proportion of the



[1]

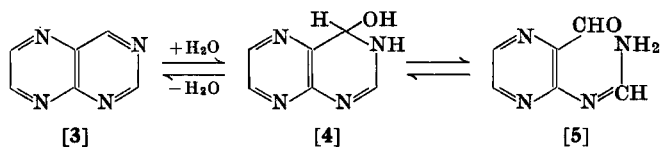


[2]

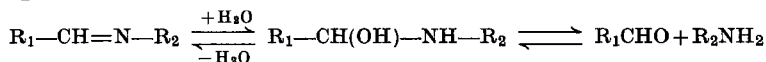
¹ See preceding article by A. Albert and W. L. F. Armarego, p. 1.

hydrated form. For example, the stable neutral molecule of quinazoline is **1**, whereas its stable cation is **2**. Acids such as 2- and 6-hydroxypteridine and 2-hydroxy-1,3,8-triazanaphthalene form stable hydrated neutral species but their anions are essentially anhydrous. Covalent hydration is further increased in the cations. For example, the cation of 6-hydroxy-7-methylpteridine is much more hydrated than the neutral molecule.

In many cases, addition or removal of water proceeds sufficiently slowly that some of the physical properties of unstable species (such as hydrated neutral quinazoline or anhydrous 2-hydroxypteridine) can be observed. In these cases, reaction kinetics can also be examined. Addition of water to pteridine is of special interest in relation to studies of the formation and hydrolysis of Schiff bases. The reaction proceeds in two reversible stages,² $3 \rightleftharpoons 4 \rightleftharpoons 5$;



compare



where R_1 and R_2 are aromatic groups.

The purpose of the present review is to indicate the methods that have been used to obtain quantitative equilibrium and kinetic data for this water-addition reaction and to discuss the results that have so far been reported. It is hoped that by describing some of the characteristics of this reaction recognition of further examples may be facilitated.

II. Physical Properties Used in Quantitative Studies

A. ELECTRONIC (ULTRAVIOLET AND VISIBLE) ABSORPTION SPECTRA

The electronic absorption spectra of heterocyclic molecules have their origins in the transitions of electrons between different molecular orbitals. In general, the more these orbitals are spread out in space, the closer together are their energy levels and the longer the wavelengths

² D. D. Perrin, *J. Chem. Soc.* 645 (1962).

at which absorption maxima occur. Addition of a molecule of water across a C=N bond would be expected to modify the observed spectrum; usually, by reducing the conjugation pathway in the molecule, it will produce spectral shifts towards shorter wavelengths. In such systems, a comparable effect on the spectrum is often produced by reduction of the —C=N— bond to —CH—NH— : the absorption maxima for 3,4-dihydro-2-hydroxypteridine and 3,4-dihydro-2,4-dihydroxypteridine ("hydrated 2-hydroxypteridine") occur at 248 ($\log \epsilon = 3.72$) and 317 $\text{m}\mu$ (3.89), and at 230 (3.88) and 307 $\text{m}\mu$ (3.83), respectively.³

However, much greater differences between the spectra of dihydro compounds and the corresponding covalently hydrated species are sometimes found. Thus, the neutral molecule of hydrated quinazoline, 3,4-dihydro-4-hydroxyquinazoline, has $\lambda_{\text{max}} = 265 \text{ m}\mu$ ($\log \epsilon = 3.97$), whereas 3,4-dihydroquinazoline has $\lambda_{\text{max}} = 291 \text{ m}\mu$ ($\log \epsilon = 3.76$), a difference of 26 $\text{m}\mu$ ⁴; for the cations the figures are 260 and 280 $\text{m}\mu$, respectively. Also, covalent hydration does not necessarily produce a hypsochromic shift. The change from pteridine to its water-adduct, 3,4-dihydro-4-hydroxypteridine, is accompanied by a bathochromic shift of about 20 $\text{m}\mu$.² Similar effects have been noted for 3-nitro- and 8-nitro-1,6-naphthyridine⁵ and for 1,4,5,8-tetraazaphthalene.⁶ The difference in the nature of the absorption spectral changes for pteridine and quinazoline may be due to an increase in the ease with which electrons on N-3 of the hydrated pteridine species can be excited into an orbital in which there is an electron transfer towards N-8. Consistent with this explanation is the hypsochromic shift of almost 30 $\text{m}\mu$ which follows protonation of hydrated pteridine.²

Addition of a proton to a nitrogen-containing heteroaromatic base usually produces only a small shift (about $\pm 5 \text{ m}\mu$) in the wavelengths of the absorption maxima. Somewhat greater effects can be produced if either the neutral base or its cation has a significant resonance stabilization that is lacking in the other, or if the band is due to an $n\text{--}\pi$ transition (leading to a hypsochromic shift on cation formation). Some systems where no such explanation is apparent nevertheless show large spectral changes in passing from the neutral molecule to the cation, and the observation of anomalous shifts of this kind in the

³ A. Albert and S. Matsuura, *J. Chem. Soc.* 5131 (1961).

⁴ A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.* 5267 (1961).

⁵ A. Albert and W. L. F. Armarego, *J. Chem. Soc.* 4237 (1963).

⁶ W. L. F. Armarego, *J. Chem. Soc.* 4304 (1963).

spectra of pteridine and quinazoline solutions was one of the main reasons for the suggestion that these cations were hydrated.^{7, 8, 9}

The smallness or the spectral changes observed between corresponding pairs of cations and neutral molecules enables the main features of the spectra of unstable species such as the "hydrated" neutral molecule or the "anhydrous" cation of pteridine to be predicted from the spectra of the "hydrated" cation and "anhydrous" neutral molecule, respectively. In this way, suitable wavelengths can readily be selected at which hydration and dehydration will produce big changes in the optical density.

TABLE I
ULTRAVIOLET SPECTRA OF SOME HYDROXYPTERIDINES IN WATER^a

Species	$\lambda_{\max}(\text{m}\mu)$; $\log \epsilon$ in parentheses ^b
2-Hydroxypteridine	
(Unstable) anhydrous neutral molecule	353 (3.84)
(Stable) anhydrous anion	224 (4.31); 265 (3.82); 375 (3.83)
(Stable) hydrated neutral molecule	232 (3.96); <u>281</u> (3.57); 308 (3.89)
(Unstable) hydrated anion	230 (3.78); 267 (3.69); 312 (3.66); <u>340</u> (3.38)
6-Hydroxypteridine	
(Unstable) anhydrous neutral molecule	237 (3.75); 335 (3.73)
(Stable) anhydrous anion	222 (4.27); 256 (3.88); 358 (3.74)
(Stable) hydrated neutral molecule	288 (3.99)
(Unstable) hydrated anion	236 (3.39); 294 (4.03)

^a Taken from Y. Inoue and D. D. Perrin, *J. Chem. Soc.* 2600 (1962).

^b Values underlined indicate inflections.

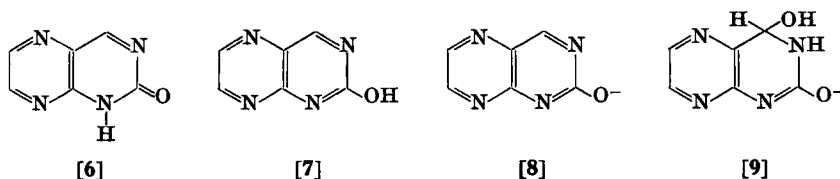
Similar considerations apply to nitrogen-containing heterocycles carrying acidic groups, for example 2-hydroxypteridine, but the situation is further complicated by lactam-lactim tautomerism in the neutral species. Thus, hydroxypteridines exist predominantly as lactams, such as **6**, in dynamic equilibrium with small amounts of lactims, such as **7**.⁷ There is, in consequence, a decrease in the aromatic

⁷ D. J. Brown and S. F. Mason, *J. Chem. Soc.* 3443 (1956).

⁸ A. Albert, *Chem. Soc. (London) Special Publ. No. 3*, 138 (1955).

⁹ A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.* 4191 (1956).

character (because, in the lactam, contributions to this property come only from some of the less energetically favored canonical forms) of the ring to which the hydroxyl group is attached. This leads to some π -electron localization, thereby predisposing the molecule towards addition of water, especially if the covalently hydrated form has



increased resonance stabilization.¹⁰ Thus the neutral molecules of 2- and 6-, but not 4- or 7-, -hydroxypteridine exist almost entirely in the hydrated form. On the other hand, formation of the anhydrous anions confers on them benzenoid-type aromaticity, thereby stabilizing them relative to the hydrated species. Hence, equilibria such as $8 + \text{H}_2\text{O} \rightleftharpoons 9$ lie well to the left. Here again, reversible hydration produces readily observable spectral differences, as may be seen from Table I.

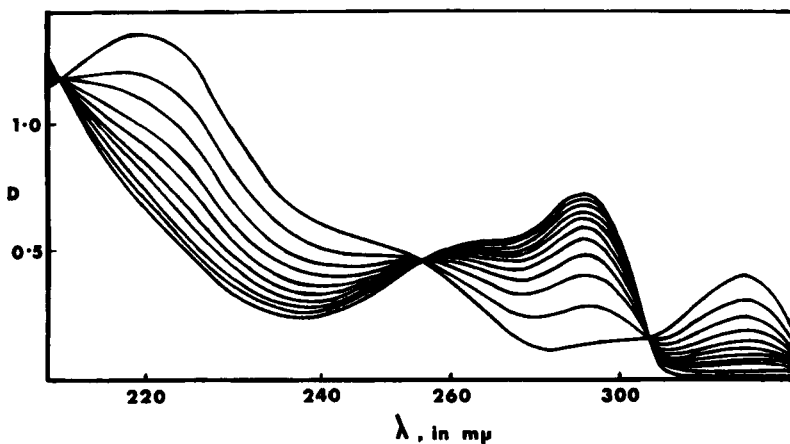


FIG. 1. Serial spectral scans following rapid neutralization of an alkaline solution of 6-hydroxy-2-methylpteridine.

¹⁰ A. Albert, in "Pteridine Chemistry" (W. Pfeleiderer and E. C. Taylor, eds.), p. 111. Pergamon Press, Oxford, 1964.

In the case of 2- and 6-hydroxypteridine and their derivatives, the anhydrous species in neutral solutions (produced by rapid addition of equilibrated alkaline solutions to neutral buffers) change sufficiently slowly into the hydrated species that serial scans on a recording spectrophotometer can be used to demonstrate the process. The results shown in Fig. 1 for 6-hydroxy-2-methylpteridine are typical.

A useful diagnostic tool for investigating possible hydration of cations of bases for which pK_a is greater than about one is the measurement of their ultraviolet spectra in aqueous acid solutions and also in an anhydrous acidic solvent such as dichloroacetic acid (for which the Hammett acidity function, H_0 , is -0.9 , and in which hydration of the cation cannot occur). This technique has been used with quinazoline to obtain spectra approximating those of the hydrated and anhydrous cations, respectively.¹¹ For weaker bases, spectral measurements in sulfuric acid–water mixtures of increasing acid content may be used to reveal a progressive conversion of hydrated into anhydrous species as the thermodynamic activity of the water decreases.

B. ACID DISSOCIATION CONSTANTS (pK_a VALUES)

Although quantitative discussion is not yet possible, some well-defined relations are apparent among the acid dissociation constants of heterocyclic species. A very useful generalization is that successive replacements of $=CH-$ groups by $=N-$ in aromatic molecules to give, for example, the mono-, di-, tri-, and tetra-azanaphthalenes, leads to a progressive lowering (base-weakening) of the pK_a of the nitrogen heterocycle. Conversely, methyl substitution in a molecule raises the observed pK_a . Table II shows some of the data on which these generalizations are based.

Some of the scatter within the groups is undoubtedly due to differences in bond order and also to whether or not the nitrogens are located in the same ring. Nevertheless, some striking exceptions are apparent in which the pK_a values are much higher than expected. These include quinazoline, 1,3,5-, 1,3,7-, 1,3,8-, and 1,4,6-triazanaphthalene, pteridine, and 1,4,5,8-tetraazanaphthalene. In all these cases, covalent hydration of the cation has been shown to occur, so the measured pK_a values are, in fact, equilibrium values involving both hydrated and anhydrous species. The hydrated species are, without

¹¹ A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.* 2689 (1961).

TABLE II
ACID DISSOCIATION CONSTANTS OF SOME AZANAPHTHALENES AT 20°^a

Species	Measured pK_a
Quinoline	4.92
Isoquinoline	5.40
1,2-Diazanaphthalene (cinnoline)	2.32
1,3-Diazanaphthalene (quinazoline)	3.46
1,4-Diazanaphthalene (quinoxaline)	0.56
1,5-Diazanaphthalene (1,5-naphthyridine)	2.84
1,6-Diazanaphthalene (1,6-naphthyridine)	3.76
1,7-Diazanaphthalene (1,7-naphthyridine)	3.61
1,8-Diazanaphthalene (1,8-naphthyridine)	3.36
2,3-Diazanaphthalene (phthalazine)	3.46
1,2,4-Triazanaphthalene	-0.82
1,3,5-Triazanaphthalene	4.11 ^b
1,3,7-Triazanaphthalene	4.70 ^b
1,3,8-Triazanaphthalene	3.85 ^b
1,4,5-Triazanaphthalene	1.20
1,4,6-Triazanaphthalene	4.56
1,3,5,8-Tetraazanaphthalene (pteridine)	4.05
1,4,5,8-Tetraazanaphthalene	2.47
Quinoline	4.92
2-Methylquinoline	5.83
3-Methylquinoline	5.17
4-Methylquinoline	5.67
5-Methylquinoline	5.20
6-Methylquinoline	5.22
7-Methylquinoline	5.34
8-Methylquinoline	5.05

^a Thermodynamic values taken from ref. 13 unless otherwise indicated.

^b W. L. F. Armarego, *J. Chem. Soc.* 4094 (1962).

exception, stronger bases than the corresponding anhydrous ones, and the observed, equilibrium, pK_a is greater than expected. In the one case where, by using sufficiently rapid experimental methods, it has been possible to obtain the true pK_a of an anhydrous base which ordinarily undergoes hydration, the value has been found to accord

with those of related but non-hydrating species. To date, these measurements have been possible only for 1,4,6-triazanaphthalene, for which the pK_a of the anhydrous species is 2.62¹² (compare 3.49 and 3.55 for 5-nitro- and 8-nitro-isoquinoline,¹³ respectively) and the pK_a of the hydrated species is 8.50.¹⁴

However, it is among heterocyclic acids such as 2- and 6-hydroxy-pteridine that the most striking effects are observed. Rapid alkali

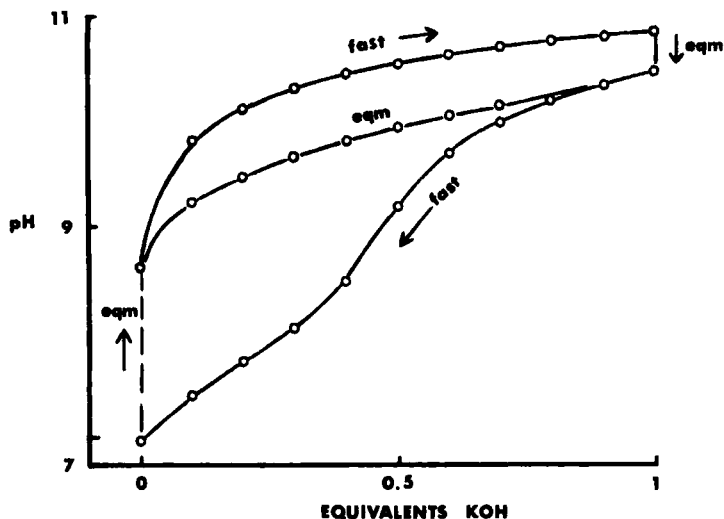


FIG. 2. Hysteresis loop in rapid titration of 0.001M 2-hydroxy-6-methylpteridine with 0.01M potassium hydroxide and back-titration with hydrochloric acid, and the equilibrium titration curve.

titration of an equilibrated neutral solution affords results from which an approximate¹⁵ acidic pK_a value for the hydrated species can be obtained, whereas rapid acid titration of an equilibrated solution of the anion gives the approximate¹⁵ pK_a of the anhydrous species. The two values differ so widely that the complete titration curve resembles a well-defined hysteresis loop. If, in either the forward- or the back-

¹² A. Albert and G. B. Barlin, *J. Chem. Soc.* 5156 (1963).

¹³ D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," *Pure Appl. Chem.*, in press.

¹⁴ D. D. Perrin and Y. Inoue, *Proc. Chem. Soc.* 342 (1960).

¹⁵ The pK_a values are approximate because the solution always contains a mixture of hydrated and anhydrous species, although one of these forms is usually present to a much greater extent.

titration, equilibrium is allowed to be reached after each addition of reagent, a curve lying between the other two curves is obtained, and from it the equilibrium pK_a can be calculated. The results for 2-hydroxy-6-methylpteridine shown in Fig. 2 are typical. As shown in Table III, the hydrated species are weaker acids (have higher pK_a values) than the corresponding anhydrous species.

TABLE III
ACID DISSOCIATION CONSTANTS OF SOME HYDRATED AND
ANHYDROUS SPECIES^a

Species	pK_a
"Hydrated 2-hydroxypteridine"	11.05
Anhydrous 2-hydroxypteridine	7.7
"Hydrated 6-hydroxypteridine"	9.90
Anhydrous 6-hydroxypteridine	6.45
"Hydrated 2-hydroxy-1,3,8-triazanaphthalene"	11.25
Anhydrous 2-hydroxy-1,3,8-triazanaphthalene	9.1

^a Taken from D. D. Perrin and Y. Inoue, *Proc. Chem. Soc.* 342 (1960).

C. POLAROGRAPHIC BEHAVIOR

The difference in the electronic structures of anhydrous and covalently hydrated pteridine leads to the appearance of two steps when neutral, or weakly acid, equilibrated pteridine solutions are polarographically reduced.¹⁶ The step for anhydrous pteridine appears at the more positive potential. Similarly, by taking serial polarograms on freshly prepared neutral pteridine solutions, the progressive approach to an equilibrium mixture of hydrated and anhydrous species can be observed, and, from the step heights at equilibrium, the concentration ratios of these species can be obtained.¹⁶ In acid solution, equilibrium is rapidly attained and a polarographically inactive product is then slowly and reversibly formed.¹⁶ This substance is the cation of the ring-opened species, 2-aminomethyleneamino-3-formylpyrazine.² 2-Aminopteridine also gives steps indicating the reversible formation

¹⁶ J. Komenda and D. Laskafeld, *Collection Czech. Chem. Commun.* 27, 199 (1962).

of a covalent hydrate.¹⁶ Polarography has been used to obtain an estimate of the degree of hydration of neutral 4-methylpteridine.¹⁷

The method, as so far developed, is limited by the condition that the hydration-dehydration reaction must proceed at a rate that is slow compared with the time needed to obtain a polarogram. In principle, the method is capable of much wider application to covalent-hydration studies if use is made of oscillographic polarographic techniques or of chronopotentiometry. These refinements are currently being investigated.

D. THE "BLOCKING" EFFECT OF A METHYL GROUP

If a methyl group replaces a hydrogen atom on the carbon of the C=N bond across which addition of water occurs, a considerable reduction in the extent of water addition is observed.^{4, 18, 19} Conversely, the existence of such a "blocking" effect can be used as a provisional indication of the site at which addition of water occurs, while the spectrum and acid dissociation constant of the methyl derivative provide a useful indication of the corresponding properties of the anhydrous parent substance. Examples of the effect of such a methyl group on equilibria are given in Table IV.

TABLE IV
THE EFFECT OF A METHYL GROUP ON THE HYDRATION EQUILIBRIUM

Substance	[hydrated n.m.]/ [anhyd. n.m.] ^a	Reference
Pteridine	0.29	2
4-Methylpteridine	0.028	17
6-Hydroxypteridine	125	14
6-Hydroxy-7-methylpteridine	1.29	31
2-Hydroxypteridine	300	14
2-Hydroxy-4,6,7-trimethylpteridine	0.4	14

^a The abbreviation "n.m." indicates neutral molecule.

¹⁷ Y. Inoue and D. D. Perrin, *J. Chem. Soc.* 2648 (1963).

¹⁸ A. Albert and F. Reich, *J. Chem. Soc.* 127 (1961).

¹⁹ W. L. F. Armarego, *J. Chem. Soc.* 561 (1962).

The considerable reduction in the extent of hydration of the quinazoline cation which results from the insertion of a 4-methyl group has been used in deriving estimates from spectral data of the extent of hydration of other quinazoline species.¹⁹

E. NUCLEAR MAGNETIC RESONANCE SPECTRA

The nuclear magnetic resonance spectrum of pteridine dissolved in heavy water changes steadily with time until equilibrium between the anhydrous and the covalently-hydrated molecules is reached.²⁰ The spectra of the two species are quite distinct and, from the measurements of peak heights, the equilibrium ratio is readily calculated. Nuclear magnetic resonance spectra have also been used to demonstrate covalent addition of water and methanol to several 1,3,6,8-tetra-azanaphthalenes (see ref. 1). The important and distinguishing property is that the addition reaction converts an unsaturated carbon atom into a saturated one so that the signal for any proton bonded to it undergoes a considerable shift up-field. (In this example the shift was about 3.8 p.p.m.) By comparisons using suitable reference substances, the technique can also be used to provide evidence to distinguish between hydrated and ring-opened species. Recently,^{20a} n.m.r. measurements have been used to demonstrate hydration of the quinazoline cation in aqueous trifluoroacetic acid. Because this method is potentially capable of being used to study reactions with exchange times down to about 0.001 sec, there is little doubt that, in the future, it will extend the accessible range of covalent hydration measurements.

III. Rapid-Reaction Apparatus

Following the original rapid-flow experiments of Hartridge and Roughton,²¹ the introduction of the stopped-flow method,²² and the use of electronic techniques for rapid recording,²³ rapid-reaction techniques have found wide application in chemistry and bio-

²⁰ S. Matsuura, personal communication (1962).

^{20a} W. L. F. Armarego and R. E. Willette, *J. Chem. Soc.*, in press.

²¹ H. Hartridge and F. J. W. Roughton, *Proc. Roy. Soc. (London)*, *Ser. A* **104**, 376 (1923).

²² F. J. W. Roughton, *Proc. Roy. Soc. (London)*, *Ser. B* **115**, 473 (1934).

²³ B. Chance, *J. Franklin Inst.* **229**, 455, 613, 737 (1940); "Rates and Mechanisms of Reactions," *Technique of Organic Chemistry*, Vol. VIII (Friess and Weissberger, eds.), p. 690. Interscience, New York, 1953.

chemistry. They have played a major role in studies of covalent hydration in nitrogen-containing heterocycles.

In these studies, the first step consisted of the replacement of the usual, visually read pH-meter with a recording instrument, so that potentiometric titrations (under nitrogen, in a thermostatted vessel, and with magnetic stirring) could be carried out much more quickly than by conventional methods. The instrument used was a Vibron model 33B Electrometer, with a pH-measuring unit model C33B attachment (Electronic Instruments Ltd.), and its output was applied directly to a Rectiriter recording milliammeter (Texas Instruments Inc.).²⁴ In this way, a titration, in which acid or base was added in 0.1 equivalents from a micrometer syringe, could be carried out in less than 3 minutes. This was adequate for demonstrating reversible hydration in the 2- and 6-hydroxypteridine series (neutral molecule and anion) and in 1,4,6-triazanaphthalene (cation and neutral molecule), and for obtaining acid dissociation constants of their hydrated, anhydrous, and equilibrium species, which, in turn, gave the equilibrium ratios of hydrated to anhydrous species.¹⁴ Nevertheless, the values obtained for 1,4,6-triazanaphthalene in the more strongly acid solutions were only approximate and have since been revised using more-rapid techniques.¹²

A much more detailed study of the hydration phenomenon, including its reaction kinetics, became possible by applying a modified Chance²³ rapid-reaction apparatus. Basically, this apparatus is a device in which two solutions can be mixed rapidly and then brought to a point at which some physical property of the mixture can be observed and recorded. Two techniques can be distinguished. In the *continuous-flow* method, the solutions flow continuously at a constant rate, so that steady-state conditions are maintained at the observation point. Depending on the dimensions of the apparatus and also on the flow rates, the solution will be observed somewhere between 0.001 and 5 sec after mixing. An application of this method is in the determination of the spectra of unstable species. The limiting factor is the requirement that the half-life of the unstable species must be appreciably greater than the time between mixing and observation. In the *stopped-flow* method, the solutions are mixed and then, suddenly, the flow of liquid through the apparatus is arrested. The time-dependent changes in the mixture located at the observation point are recorded. This technique, which requires much less material, can be applied to study

²⁴ D. D. Perrin, *J. Chem. Soc.* 3189 (1960).

the kinetics of reactions by observing optical density changes at a suitable wavelength. Similarly, by using a series of buffers of known pH, to which the appropriate acid, alkaline, or neutral solution of the otherwise unstable species is rapidly added, the acid dissociation constant of an unstable species can be determined using this method. Measurement of optical density changes with time permits back-

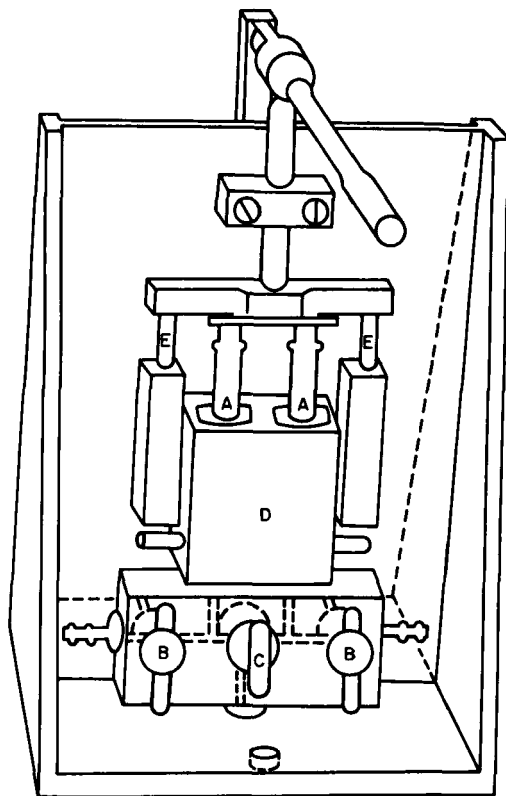


FIG. 3. Diagram of mixing unit of rapid-reaction apparatus used in covalent-hydration studies.

extrapolation to the time of mixing, so that more precise extinction coefficient values of unstable species or mixtures can be obtained. This technique, applied in turn at a number of different wavelengths, can be used to afford an accurate absorption spectrum of an unstable species, e.g. the hydrated neutral quinazoline molecule formed by rapidly mixing a solution of hydrated quinazoline cation with a neutral

buffer. All these techniques have been used in studying reversible hydration in nitrogen-containing heterocycles.

The apparatus constructed in our laboratory and used for this work consists of a mixing unit, shown in Fig. 3, to the under-side of which either of two interchangeable observation units can be attached by two knurled bolts. One of these units has as its detecting device a glass micro-electrode so that, in conjunction with a suitable recorder, it can be used for following rapid pH changes. The other unit consists of a 1-cm quartz cell designed to fit directly into a Shimadzu Model RS27 recording spectrophotometer. The cell is housed in a Perspex and metal block through which water circulates. Freshly mixed solution enters the cell through a narrow nylon tube attached near its base and leaves by another tube attached near its top. The technique is obviously capable of extension, for example, by the use of thermistors to follow reactions involving heat changes or of platinum electrodes to study rapid conductivity changes.

The mixing unit consists of two 10 ml nylon syringes (A) connected, on one hand, to three-way taps (B), for rinsing and for filling from reservoirs, and, on the other, to the mixing chamber which is housed in a three-way Perspex tap (C), bedded into a Teflon sleeve. The nylon syringes are mounted in a hollow metal block (D) through which water circulates at a controlled temperature. The plungers of the syringes are attached to a metal crossbar which can be raised or lowered by a lever, so that the syringes can be filled or emptied simultaneously. This crossbar is positioned by two guide rods (E) fixed at its ends. The mixing chamber is formed by drilling a hole several millimeters in diameter into the tap and then partially filling the hole by sealing into it a short length of rigid Perspex tubing. Liquids from each syringe enter the mixing chamber through a pair of jets arranged tangentially to the chamber, so as to impart a very rapid circular motion without excessive turbulence.

For *continuous-flow* studies, liquid is allowed to flow, under gravity, from the two reservoirs (filled to the same level) through the mixing chamber and the observation cell, the exit tube being carried down to near floor level to provide adequate hydrostatic pressure. In this way, the liquid in the cell at any time corresponds to conditions between 1 and 2 sec after mixing. In *stopped-flow* measurements, the shortest attainable time is still several tenths of a second after mixing. The limiting factor in both methods is the time taken to drive through the

apparatus the relatively large volume of liquid needed in the observation cell. By replacing this cell with a quartz capillary tube and using a cathode ray oscilloscope to record sudden optical density changes, this technique is capable of extension into the millisecond range. This should, among other things, enable the pK_a values of the unstable anhydrous cations of organic bases such as quinazoline to be determined. A need for such a more-rapid technique exists in the study of hydration and dehydration reactions of lumazine and its methyl derivatives, because the rates are too fast to permit reliable conclusions to be drawn from data obtained with the apparatus presently available.

IV. Mathematical Relations

A. EQUILIBRIA

In systems such as the 2- and 6-hydroxypteridine series, rapid potentiometric or spectrophotometric pK_a determinations on neutral solutions usually give values near to the acidic pK_a of the hydrated series. (Exceptions include 2-hydroxy-4,6,7-trimethyl-,¹⁴ 6-hydroxy-7-methyl-,¹⁴ and 4,6-dihydroxy-pteridine,²⁵ where the neutral solution contains comparable amounts of hydrated and anhydrous species. In such cases, rapid potentiometric titrations show two well-defined and separated curves, one for the hydrated, the other for the anhydrous, species.) Similarly, from solutions of the anion, an approximate pK_a value for the anhydrous species is obtained. For convenience, the anhydrous molecule is referred to as HX, its anion as X^- , the hydrated neutral molecule as HY, and its anion as Y^- , and the two equilibrium constants are defined as follows:

$$K_1 = [Y^-]_{\text{eqm}}/[X^-]_{\text{eqm}} \quad (1)$$

$$K_2 = [HY]_{\text{eqm}}/[HX]_{\text{eqm}} \quad (2)$$

corresponding to the reactions $X^- + H_2O \rightleftharpoons Y^-$ and $HX + H_2O \rightleftharpoons HY$, respectively.

By carrying out the pK_a determination very slowly, so that equilibrium is reached at every point, an equilibrium pK_a value is obtained, for which

$$(K_a)_{\text{eqm}} = \frac{(a_{H^+})([X^-]_{\text{eqm}} + [Y^-]_{\text{eqm}})}{[HX]_{\text{eqm}} + [HY]_{\text{eqm}}} \quad (3)$$

²⁵ Y. Inoue and D. D. Perrin, *J. Chem. Soc.* 2600 (1962).

Substitution of Eqs. (1) and (2) into Eq. (3) gives Eq. (4):

$$\begin{aligned}(\text{p}K_a)_{\text{eqm}} &= \text{p}K_a^{\text{X}} + \log(1 + K_2)/(1 + K_1) \\ &= \text{p}K_a^{\text{Y}} - \log\left(\frac{K_2(1 + K_1)}{K_1(1 + K_2)}\right).\end{aligned}\quad (4)$$

These equations, on rearrangement, give expressions for K_1 and K_2 that can be evaluated from experimental data:

$$K_1 = \frac{K_a^{\text{Y}}(K_a^{\text{X}} - (K_a)_{\text{eqm}})}{K_a^{\text{X}}((K_a)_{\text{eqm}} - K_a^{\text{Y}})} \quad (5)$$

$$K_2 = \frac{K_a^{\text{X}} - (K_a)_{\text{eqm}}}{(K_a)_{\text{eqm}} - K_a^{\text{Y}}}. \quad (6)$$

From Eqs. (5) and (6), values of K_1 and K_2 can be obtained and used to correct the initial estimates of $\text{p}K_a^{\text{X}}$ and $\text{p}K_a^{\text{Y}}$ for the (usually low) concentrations of the other species present. These new $\text{p}K_a$ values can be used to refine K_1 and K_2 , the process being repeated until constancy is achieved. One cycle is usually sufficient. In the case where $\text{p}K_a^{\text{X}}$, $(\text{p}K_a)_{\text{eqm}}$, and $\text{p}K_a^{\text{Y}}$ are separated by at least one pH unit, so that $K_1 \leq 0.1$ and $K_2 \geq 10$, the approximations can be made that

$$-\log K_1 \approx \text{p}K_a^{\text{Y}} - (\text{p}K_a)_{\text{eqm}} \quad (7)$$

and

$$\log(1 + K_2) \approx (\text{p}K_a)_{\text{eqm}} - \text{p}K_a^{\text{X}}. \quad (8)$$

Similar equations can be derived for analyzing the titration curves of species which can form both mono- and di-anions.

For an organic base, X, which can undergo covalent hydration, the corresponding equilibrium constants are

$$K_2 = [\text{Y}]_{\text{eqm}}/[\text{X}]_{\text{eqm}} \quad (9)$$

and

$$K_3 = [\text{HY}^+]_{\text{eqm}}/[\text{HX}^+]_{\text{eqm}}. \quad (10)$$

Formation of the hydrated species is more favored in the cation than in the neutral species, and using rapid-reaction techniques the approximate $\text{p}K_a$ of the hydrated species is obtained by neutralizing acid solutions. Conversely, the approximate $\text{p}K_a$ of the anhydrous species is, in principle, obtainable by rapid acidification of solutions containing the neutral molecules. In the same way as for Eq. (4), it may readily be deduced that

$$\begin{aligned}(\text{p}K_a)_{\text{eqm}} &= \text{p}K_a^{\text{X}} + \log((1 + K_3)/(1 + K_2)) \\ &= \text{p}K_a^{\text{Y}} - \log\left(\frac{K_3(1 + K_2)}{K_2(1 + K_3)}\right),\end{aligned}\quad (11)$$

and the expressions for K_2 and K_3 are

$$K_2 = \frac{K_a^Y(K_a^X - (K_a)_{eq})}{K_a^X((K_a)_{eq} - K_a^Y)} \quad (12)$$

and

$$K_3 = \frac{K_a^X - (K_a)_{eq}}{(K_a)_{eq} - K_a^Y}. \quad (13)$$

Similarly, if $K_2 \leq 0.1$ and $K_3 \geq 10$,

$$-\log K_2 \approx pK_a^Y - (pK_a)_{eqm} \quad (14)$$

and

$$\log(1 + K_3) \approx (pK_a)_{eqm} - pK_a^X. \quad (15)$$

Very few pK_a values are known for anhydrous organic bases which can undergo covalent hydration, so that, in general, K_2 and K_3 for such systems cannot be calculated using Eqs. (12) and (13). However, in cases where the pK_a of the hydrated species can be measured, Eq. (14) can be used to obtain an approximate estimate of K_2 , the equilibrium ratio of hydrated to anhydrous neutral molecules. This treatment has been applied to quinazoline, the nitroquinazolines, and some triazanaphthalenes.²⁶

In principle, if an estimate could be made of K_3 , the equilibrium concentration ratio of hydrated to anhydrous cations, relation (15) would enable the approximate pK_a of the anhydrous species to be calculated. Although such an estimate may be derivable from absorption spectral data, no such calculation appears to have been reported. Conversely, if an upper estimate of pK_a^X is made from the $(pK_a)_{eqm}$ value for the corresponding, appropriately methyl-substituted base, Eq. (15) can be used to furnish a lower limit to the extent of hydration in the cation. Taking quinazoline as an example:

$$(pK_a)_{eqm} \text{ for 4-methylquinazoline} = 2.52 \text{ at } 20^\circ \text{C.}^{11}$$

Approximate pK_a exaltation due to methyl group, 0.7 (from pyrimidine and 4-methylpyrimidine¹³).

$$\therefore (pK_a^X)_{max} \text{ for quinazoline} = 1.8.$$

$$\text{But } (pK_a)_{eqm} \text{ for quinazoline} = 3.51 \text{ at } 20^\circ.^{11}$$

$$\therefore \text{For quinazoline, } [HY^+]_{eqm}/[HX^+]_{eqm} \geq 50.$$

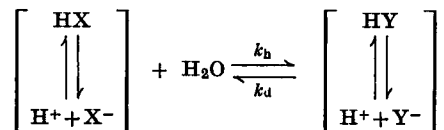
²⁶ W. L. F. Armarego, *J. Chem. Soc.* 4094 (1962).

B. KINETICS

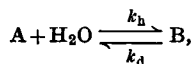
The reversible hydration of nitrogen-containing heterocyclic bases and their hydroxy and mercapto derivatives is acid-base catalyzed and, at constant pH, the reactions obey first-order rate equations.^{2, 17, 25, 27-33}

In systems such as the 2- and 6-hydroxypteridines, sudden addition of an alkaline solution to a neutral buffer, or of a neutral solution to an alkaline buffer, displaces the equilibrium between hydrated and anhydrous species (because the anions are less hydrated than the neutral molecules). By measuring the time-dependent change of optical density at a selected wavelength, a first-order rate constant, k_{obs} , can be obtained. This constant is a composite one, and to see its relationship to other quantities some discussion is necessary.

Equilibria in these solutions can be summarized by the scheme



where the species within the brackets exist in dynamic equilibrium. (Lactam-lactim tautomerism, involving only a proton transfer between a nitrogen and an oxygen atom, may also occur, but, if so, its rate is too fast to be detected by the methods used in studying the hydration reaction.) At constant pH, the $[\text{HX}]/[\text{X}^-]$ and $[\text{HY}]/[\text{Y}^-]$ ratios are constant and equal to $(a_{\text{H}^+})/K_a^{\text{X}}$ and $(a_{\text{H}^+})/K_a^{\text{Y}}$, respectively, so that the system can be treated as if it were



where $[\text{A}] = [\text{X}^-] + [\text{HX}]$, and $[\text{B}] = [\text{Y}^-] + [\text{HY}]$.

In such a system the rate of change of optical density, k_{obs} , is a

²⁷ Y. Inoue and D. D. Perrin, *J. Chem. Soc.* 3936 (1963).

²⁸ Y. Inoue and D. D. Perrin, *J. Chem. Soc.* 4803 (1963).

²⁹ A. Albert, Y. Inoue, and D. D. Perrin, *J. Chem. Soc.* 5151 (1963).

³⁰ Y. Inoue and D. D. Perrin, *J. Chem. Soc.* 5166 (1963).

³¹ Y. Inoue, Ph.D. Thesis, Australian National University (1963).

³² Y. Inoue and D. D. Perrin, *J. Phys. Chem.* **66**, 1689 (1962).

³³ A. Albert and C. F. Howell, *J. Chem. Soc.* 1591 (1962).

constant ($= k_h + k_d$), irrespective of whether one measures changes starting from pure A or pure B. Therefore it is possible to obtain equilibrium ratios of hydrated to anhydrous species from kinetic measurements. 6-Chloropteridine is an example where the neutral molecule is appreciably hydrated at equilibrium, but the ratio of the two species cannot be determined by direct measurement because slow hydrolysis supervenes. Hydration is virtually complete in the cation, so that its rapidly neutralized solution affords the hydrated neutral molecule, whereas freshly dissolved 6-chloropteridine is essentially anhydrous. By selecting a series of values for D_{eqm} for insertion into the equation

$$-dD/dt = k_{\text{obs}}(D - D_{\text{eqm}}),$$

(where D is the measured optical density at a wavelength for which the extinction coefficients of hydrated and anhydrous neutral molecules are sufficiently different), it is possible very quickly to find the value of D_{eqm} that is necessary to ensure equality of the k_{obs} value for the rates of dehydration and hydration over an initial limited period during which side reactions are negligible. (These measurements must be made at the same temperature and ionic strength.) This technique is very sensitive to choice of D_{eqm} , hence this quantity can be accurately calculated. Knowing D_{eqm} , the ratio of hydrated to anhydrous species is readily obtained from Eq. (15a):

$$\frac{D_{\text{anhydr}} - D_{\text{eqm}}}{D_{\text{eqm}} - D_{\text{hydr}}} = \frac{[A]_{\text{eqm}}}{[B]_{\text{eqm}}} = \frac{k_h}{k_d}. \quad (15a)$$

If these measurements are made at a pH where only the neutral molecules are present, the ratio is equal to the constant K_2 . This restriction about pH is necessary because k_h and k_d are ordinarily composite, their relationship to the equilibrium constants and pK values being given by the relevant equations,³²

$$k_h = k_{\text{obs}} \left(\frac{K_2(a_{\text{H}^+}) + K_1 K_a^{\text{x}}}{(1 + K_2)(a_{\text{H}^+}) + (1 + K_1)K_a^{\text{x}}} \right) \quad (16)$$

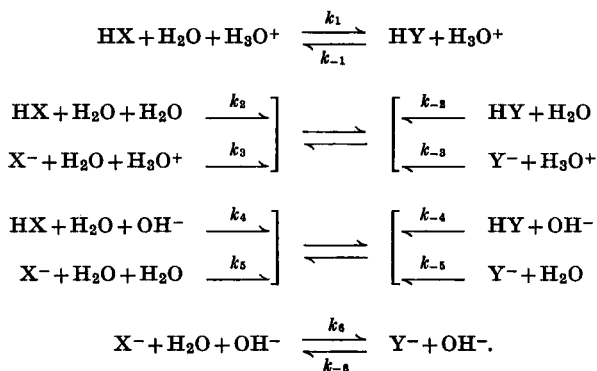
and

$$k_d = k_{\text{obs}} \left(\frac{(a_{\text{H}^+}) + K_a^{\text{x}}}{(1 + K_2)(a_{\text{H}^+}) + (1 + K_1)K_a^{\text{x}}} \right), \quad (17)$$

where $K_1 = [\text{Y}^-]_{\text{eqm}}/[\text{X}^-]_{\text{eqm}}$, and $K_2 = [\text{HY}]_{\text{eqm}}/[\text{HX}]_{\text{eqm}}$.

But pH-rate profiles suggest that k_h and k_d are composite constants

for simultaneous reactions in which there is catalysis of hydration of HX and X⁻ and dehydration of HY and Y⁻ by solvent and by hydronium and hydroxyl ions. These reactions follow:



Because of the dynamic equilibrium between neutral species and their anions, the rate constants for reactions 2 and 3 and those for reactions 4 and 5 cannot be evaluated separately. The relation between k_h and the above constants is ²⁷

$$k_h(K_a^X + (a_{H^+})) = k_1(a_{H^+})^2 + (k_2[\text{H}_2\text{O}] + k_3K_a^X)(a_{H^+}) + k_4K_w + k_5K_a^X[\text{H}_2\text{O}] + k_6K_a^XK_w/(a_{H^+}), \quad (18)$$

where K_2 is the dissociation constant of water. At very low reaction rates, catalysis by buffer species such as bicarbonate ion and boric acid is significant in 2-hydroxypteridine solutions,³² but, for simplicity of discussion, rate constants for such reactions are omitted in Eq. (18). The corresponding constants for the dehydration reaction are readily obtained by dividing k_1 , k_2 , and k_4 by K_2 , and k_3 , k_5 , and k_6 by K_1 .

For the acid-base catalyzed hydration and dehydration of organic bases, such as pteridine, the equations for k_h and k_d are ¹⁷

$$k_h = \frac{k_{\text{obs}}(K_a^Y + (a_{H^+}))K_2}{K_a^Y(1 + K_2) + (a_{H^+})K_2} \quad (19)$$

and

$$k_d = \frac{k_{\text{obs}}K_a^Y}{K_a^Y(1 + K_2) + K_2(a_{H^+})}, \quad (20)$$

where $K_2 = [\text{Y}]_{\text{eqm}}/[\text{X}]_{\text{eqm}}$. These rate constants can be expressed as the sums of constants in the same way as was described for the

organic acids. However, because the pK_a value of the anhydrous species usually lies far below the pH range in which hydration is studied, the anhydrous cation can be neglected in discussing the stoichiometry of the reaction. On the other hand, concentrations of the hydrated cation are significant under conditions where dehydration is observed.

In studies of the hydration and dehydration of pteridine and the methylpteridines, k_d , but not k_h , levelled out as solutions were made more acid.¹⁷ This was explained by assuming that hydronium ion catalysis of the reactions proceeded only by the formation of the cations of HY^+ and HX^+ , respectively. This effect is strikingly shown by 1,3,8-triazanaphthalene, for which the pH-rate profile of k_d is V-shaped between pH 6.82 and 10.29 but levels out and remains constant from pH 5.3 down to, at least, 2.4.³⁰

V. Equilibrium Ratios

Tables V and VI contain all the equilibrium constants so far reported for nitrogen-containing heterocycles that undergo reversible covalent hydration. Table V comprises equilibria involving hydration in cations and neutral molecules, and Table VI deals with systems of neutral molecules and anions.

Although, as Table V indicates, many examples are now known where heterocyclic cations are "largely" covalently hydrated, except for 1,4,6-triazanaphthalene and, perhaps, quinazoline, there are no reasonable accurate equilibrium constants for such systems. However, assuming these substances to be representative, the free energy change for the reaction $HX^+ + H_2O \rightleftharpoons HY^+$ can be calculated from the relation $-\Delta G = RT \ln K$ to be about 3 kcal/mole. This estimate of the maximum free energy change in hydrated cation formation is unlikely to be widely in error: even if the ratio of $[HY^+]_{eqm}/[HX^+]_{eqm}$ is 1000/1, $-\Delta G$ is only 4.5 kcal/mole. Similarly, among the hydrating neutral molecules listed in Table VI, the highest ratio of $[HY]_{eqm}/[HX]_{eqm}$ (400 for 2,6-dihydroxypteridine) corresponds only to $-\Delta G = 3.6$ kcal/mole. These figures indicate that a rather sensitive interrelation of a number of factors is involved in determining whether or not detectable hydration will occur in any particular case. A qualitative discussion of these factors has already been given.¹ In general, hydration will not be detected if in the most strongly hydrated species (cation or neutral molecule) it does not exceed about 2%.

TABLE V
HETEROCYCLIC BASES KNOWN TO HYDRATE REVERSIBLY

Base	$K_2 (= [Y]_{\text{eqm}}/[X]_{\text{eqm}})$	$K_3 (= [HY^+]_{\text{eqm}}/[HX^+]_{\text{eqm}})$	Reference
Quinazoline	5.5×10^{-5}	100 (estimated)	4
5-Amino-	—	~ 9	19
6-Amino-	—	large	19
7-Amino-	—	small	19
8-Amino-	—	~ 9	19
5-Chloro-	—	large	19
6-Chloro-	—	large	19
7-Chloro-	—	large	19
8-Chloro-	—	large	19
6,8-Dichloro-	—	large	19
2-Hydroxy-	0.33	—	33
5-Hydroxy-	—	appreciable	19
6-Hydroxy-	—	appreciable	19
7-Hydroxy-	—	small	19
8-Hydroxy-	—	appreciable	19
2-Methoxy-	—	0.56	19
5-Methoxy-	—	> 7, > 19	19
6-Methoxy-	—	> 6, > 16	19
7-Methoxy-	—	> 0.28	19
8-Methoxy-	—	large	19
2-Methyl-	—	—	19
(3-Methylquinazolinium ion)	—	—	4
4-Methyl-	—	> 0.23	19
5-Methyl-	—	> 9, > 24	19
6-Methyl-	—	> 12, > 19	19
7-Methyl-	—	—	19
8-Methyl-	—	> 9, > 16	19
2,4-Dimethyl-	—	> 0.32	19
5-Nitro-	0.0021	large	26

6-Nitro-	0.0015	large	26
7-Nitro-	0.0080	large	26
8-Nitro-	0.010	large	26
Quinazoline-3-oxide	—	large	34
7-Chloro-	—	large	34
5-Methoxy-	—	appreciable	34
6-Methoxy-	—	appreciable	34
8-Methoxy-	—	large	34
7-Methyl-	—	large	34
3-Nitro-1,6-naphthyridine	—	appreciable	5
8-Nitro-1,6-naphthyridine	—	large	5
1,3,5-Triazanaphthalene	0.0045	> 9, ($\sim 10^3$)	26
1,3,6-Triazanaphthalene	—	> 9	26
1,3,7-Triazanaphthalene	0.023	> 9, ($\sim 10^3$)	26
1,3,8-Triazanaphthalene	0.0020	> 29, ($\sim 10^3$)	30
1,4,5-Triazanaphthalene, 2-hydroxy-	—	16	34a
1,4,6-Triazanaphthalene	0.0001	95	12
3-Methyl-	9×10^{-6}	9	12
2,3-Dimethyl-	very small	very small	31
Pteridine	0.29	large	2
2-Amino-	—	—	16, 34b
6-Amino-	—	—	31
6-Chloro-	—	—	35
2-Methyl-	0.36	large	2
4-Methyl-	0.028	large	17
7-Methyl-	0.040	large	2
1,4,5,8-Tetraazanaphthalene	—	large	6
2-Methyl-	—	large	6
2,3-Dimethyl-	—	large	6
2-Amino-8-azapurine	—	—	35a

³⁴ W. L. F. Armarego, *J. Chem. Soc.* 5030 (1963).

^{34a} A. Albert and G. B. Barlin, *J. Chem. Soc.* 5737 (1963).

^{34b} A. Albert, C. F. Howell, and E. Spinner, *J. Chem. Soc.* 2595 (1962).

³⁵ J. Clark, personal communication (1963).

^{35a} A. Albert, personal communication (1963).

TABLE VI
EQUILIBRIUM RATIOS FOR HETEROCYCLIC ACIDS THAT HYDRATE REVERSIBLY

Substance	$K_1 (= [Y^-]_{\text{eqm}}/[X^-]_{\text{eqm}})$	$K_2 (= [HY]_{\text{eqm}}/[HX]_{\text{eqm}})$	Reference
2-Hydroxy-1,3,8-triazanaphthalene	0.063	9	14
3-Hydroxy-1,4,6-triazanaphthalene	0.00016	0.45	31
2-Hydroxypteridine	0.14	320	25
4-Methyl-	0.014	6	25
6-Methyl-	0.10	110	25
7-Methyl-	0.058	35	25
6,7-Diethyl-	0.055	42	27
6,7-Dimethyl-	0.046	70	25
4,6,7-Trimethyl-	0.0004	0.42	25
6-Hydroxypteridine	0.045	125	14
2-Methyl-	0.028	80	14
4-Methyl-	0.016	75	14
7-Methyl-	0.001	1.29	31
2-Mercaptopteridine	0.24	380	25
2,6-Dihydroxypteridine ^a	0.57	400	25
4,6-Dihydroxypteridine ^b	0.06	1.24	25
2-Amino- ^c (xanthopterin)	0.009	1.01	25

^a For dianions, ratio is 0.14.

^b For dianions, ratio is 0.0017.

^c For dianions, ratio is 0.0019.

VI. Results of Kinetic Measurements

The pH-rate profile for the hydration of 2-hydroxypteridine at 20° shown in Fig. 4 is typical for the heterocyclic acids listed in Table VI. Some representative values of k_h and k_d are given in Table VII. The function plotted in the figure follows from Eq. (18), and the deviations

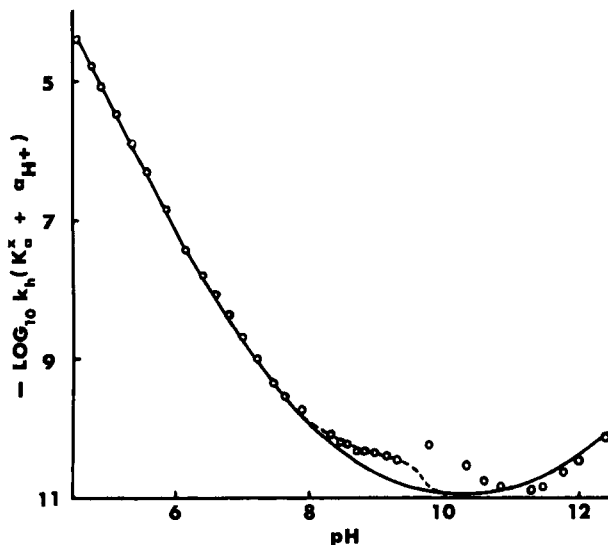


FIG. 4. The pH-rate profile for the hydration of 2-hydroxypteridine at 20°. Deviations at low rates are due to catalysis by boric acid and bicarbonate ion present in the buffers.

at low rates are due to catalysis by boric acid and bicarbonate ion in the buffers used.³² The pH-rate profiles for some representative acids, expressed in the form

$$k_h((a_{H^+}) + K_a^X) = \alpha(a_{H^+})^2 + \beta(a_{H^+}) + \gamma + \delta/(a_{H^+})$$

and

$$k_d((a_{H^+}) + K_a^Y) = \alpha'(a_{H^+})^2 + \beta'(a_{H^+}) + \gamma' + \delta'/(a_{H^+})$$

are summarized in Table VIII. Rate constants are given in reciprocal seconds.

The effects of alkyl substituents in positions 6 and 7 on the rates of hydration and dehydration of 2-hydroxypteridine are not very great. The observed decrease in the equilibrium ratio of $[HY]/[HX]$ has been

TABLE VII
CONSTANTS IN RATE EQUATION (IN SEC⁻¹) AT SELECTED pH VALUES^a

Substance	pH 4.8		pH 6.3		pH 8.1		pH 10.1		pH 11.8	
	k_h	k_d	k_h	k_d	k_h	k_d	k_h	k_d	k_h	k_d
2-Hydroxypteridine	1.01	0.00316	0.0474	0.000155	0.00451	0.0000495	—	—	0.00117	0.00697
6-Methyl-	3.06	0.0277	0.0492	0.000457	—	—	0.00118	0.00122	0.00130	0.0114
7-Methyl-	0.927	0.0266	0.0442	0.00129	0.00228	0.000133	0.000671	0.00161	0.000771	0.0118
6,7-Dimethyl-	0.855	0.0116	0.0352	0.000493	0.00148	0.000482	0.000745	0.00118	0.00155	0.0272
6,7-Diethyl-	0.865	0.0208	—	—	0.00163	0.0000832	0.0005	0.0012	0.00138	0.0223
2-Mercaptopteridine	0.755	0.00202	0.0512	0.000216	0.00148	0.000145	0.0005	0.001	0.00419	0.0174
6-Hydroxypteridine	0.0281	0.000220	0.0016	0.000021	0.00028	0.00009	0.000569	0.00718	—	—
2-Methyl-	0.0572	0.000612	0.00173	0.0000289	0.000236	0.0000910	0.000360	0.00787	0.0102	0.350
4-Methyl-	0.0293	0.000381	0.00126	0.0000316	—	—	0.000234	0.00794	0.00811	0.511
7-Methyl-	0.00641	0.00497	0.000318	0.000285	0.000047	0.00040	0.0000721	0.0244	—	—
2-Hydroxy-1,3,8-triazanaphthalene	1.08	0.120	0.0467	0.00520	0.00171	0.000208	0.00147	0.00153	0.00393	0.0478
3-Hydroxy-1,4,6-triazanaphthalene	0.00497	0.0110	0.000225	0.000548	0.0000158	0.000241	0.0000200	0.0201	0.000150	0.841

^a Taken from Y. Inoue and D. D. Perrin, *J. Chem. Soc.* 3936, 4803 (1963).

TABLE VIII
CONSTANTS IN RATE EQUATIONS^a

Substance	Hydration					Dehydration				
	α	β	γ	δ	pK_a^x	α'	β'	γ'	δ'	pK_a^y
2-Hydroxypteridine	6.3×10^4	1.1×10^{-2}	1.0×10^{-11}	3.0×10^{-23}	7.7	1.96×10^2	3.42×10^{-5}	3.11×10^{-14}	9.34×10^{-28}	11.05
6-Methyl-	1.15×10^5	3.34×10^{-3}	3.54×10^{-12}	2.69×10^{-23}	7.95	1.05×10^3	3.04×10^{-5}	3.22×10^{-14}	2.40×10^{-25}	11.00
7-Methyl-	6.49×10^4	2.66×10^{-3}	1.85×10^{-12}	1.10×10^{-23}	8.05	1.86×10^3	7.63×10^{-5}	5.32×10^{-14}	3.01×10^{-25}	10.85
6,7-Dimethyl-	5.41×10^4	1.99×10^{-3}	3.73×10^{-12}	3.34×10^{-23}	7.95	7.41×10^2	2.73×10^{-5}	5.11×10^{-14}	4.57×10^{-25}	11.15
6,7-Diethyl-	6.73×10^4	2.55×10^{-3}	2.95×10^{-12}	2.28×10^{-23}	8.04	1.62×10^3	6.14×10^{-5}	7.12×10^{-14}	5.48×10^{-25}	10.92
2-Mercaptopteridine	6.92×10^4	3.49×10^{-2}	4.09×10^{-11}	2.41×10^{-21}	6.52	1.84×10^2	9.28×10^{-5}	1.09×10^{-13}	6.43×10^{-24}	9.72
6-Hydroxypteridine	1.81×10^3	9.81×10^{-4}	1.13×10^{-11}	1.03×10^{-20}	6.45	1.38×10	7.49×10^{-6}	8.63×10^{-13}	7.77×10^{-23}	9.90
2-Methyl-	3.45×10^3	8.83×10^{-4}	4.16×10^{-11}	4.59×10^{-21}	6.53	3.63×10	9.28×10^{-6}	4.37×10^{-13}	4.78×10^{-23}	10.05
4-Methyl-	1.96×10^3	1.19×10^{-3}	6.49×10^{-11}	5.79×10^{-21}	6.3	2.46×10	1.49×10^{-5}	8.14×10^{-13}	7.10×10^{-23}	10.0
7-Methyl-	3.99×10^2	8.80×10^{-5}	3.15×10^{-12}	3.06×10^{-22}	7.09	3.09×10^2	6.82×10^{-5}	2.44×10^{-12}	2.40×10^{-22}	10.02
2-Hydroxy-1,3,8-triazanaphthalene	8.59×10^4	8.42×10^{-4}	8.29×10^{-13}	4.77×10^{-24}	9.1	9.55×10^3	9.35×10^{-5}	9.21×10^{-14}	5.36×10^{-25}	11.25
3-Hydroxy-1,4,6-triazanaphthalene	32.6×10^2	6.17×10^{-5}	9.72×10^{-13}	1.49×10^{-23}	7.32	7.24×10^2	1.37×10^{-4}	2.16×10^{-12}	3.39×10^{-23}	10.76

^a Taken from refs. 27-31.

ascribed, mainly, to a decrease in the activation energy for the dehydration reaction, so that the water-adduct reverts more quickly to the "anhydrous" species.²⁷

Substances in the 2-hydroxypteridine series, including 2-hydroxy-1,3,8-triazanaphthalene, hydrate and dehydrate about thirty times

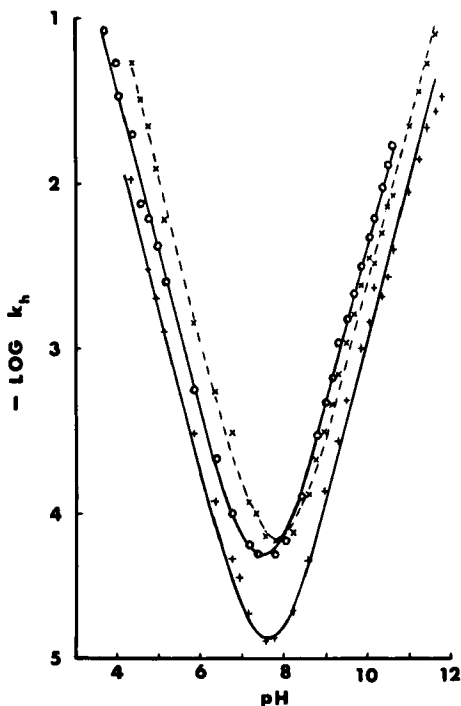
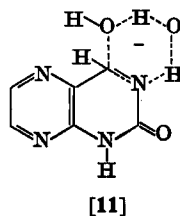
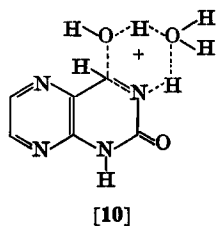


FIG. 5. The pH-rate profiles at 20° and an ionic strength of 0.1 for the reversible hydration of (○) pteridine, (×) 2-methylpteridine, and (+) 7-methylpteridine.

faster than the corresponding 6-hydroxypteridine derivatives, including 3-hydroxy-1,4,6-triazanaphthalene. This indicates that a lower activation energy is required for 3,4-addition to 2-hydroxypteridine than for 7,8-addition to 6-hydroxypteridine.

When the rates of hydration of pteridine and its methyl derivatives are plotted against pH, a similar V-shaped curve (Fig. 5) is obtained. Results for a limited series of rate measurements on the hydration of pteridine, measured polarographically,¹⁶ accord with these values.

The acid-base catalyzed hydration of pteridine and 2- and 6-hydroxypteridines may involve the formation of cyclic activated complexes of the types shown in **10** and **11** for the acid- and base-catalyzed reactions of 2-hydroxypteridine.³² In these formulations, a proton is bonded to N-3 while, at the same time, an oxygen atom of a water molecule or a hydroxyl ion is attached to C-4. Such structures are analogous to those postulated for the acid-base catalyzed hydrolysis of esters and amides.³⁶ However, an alternative formulation of **10** can be written in which the positive charge is located on N-3 so that the cyclic activated complex involves two water molecules instead of a water molecule and a hydronium ion. The non-participation of the oxygen atom of 2-hydroxypteridine in the formation of the activated complex is suggested by the closeness of the pairs of values of k and k_{-1} for 2-hydroxy- and 2-mercapto-pteridine.²⁷ This interpretation would make the ease of formation of the activated complex from the anhydrous species depend on the proton affinity of N-3 and on the net positive charge on C-4, whereas formation from the hydrated species would depend on the abilities of the hydroxyl group on C-4 and the proton on N-3 to form hydrogen bonds to the same water molecule or hydroxyl ion. Hence no simple generalizations describing the effects of substituents on individual rate constants are to be expected.



It is the rapid increase in rates of hydration with increasing hydrogen ion concentration that prevents measurement with existing apparatus of the pK_a values of anhydrous bases such as pteridine. For example, at pH 1, hydration of the anhydrous cation is half-complete in 0.01 sec at 20°. Conversely, it is the comparative slowness of the reactions in near-neutral solutions that makes it possible, by adding acid solutions to near-neutral buffers, using the stopped-flow technique, to determine the pK_a values of the hydrated species.

Knowledge of the kinetics of the reactions is often helpful in

³⁶ K. J. Laidler and P. A. Landskroener, *Trans. Faraday Soc.* **52**, 200 (1956).

elucidating the equilibria involved in hydration-dehydration phenomena. This, if several isosbestic points persist throughout the course of a reaction in which the absorption spectrum is changing steadily with time, and the rate of change of optical density indicates first-order kinetics, this is strong presumptive evidence for the direct conversion of one species into another. Similarly, an increase in optical density at any wavelength, followed by a decrease, indicates that at least two reactions are involved. These facts helped elucidate the anomalous hydration behavior of 2,6-dihydroxypteridine.²⁹

2,6-Dihydroxypteridine was expected to undergo hydration but, *a priori*, it was difficult to decide whether covalent hydration would occur across the 3,4- or the 7,8-position, or both. Kinetic and spectroscopic evidence²⁹ now indicate that addition of water occurs much more rapidly across the 3,4-positions (and, hence, that the energy of activation must be less for this site), but the 7,8-water-adduct is thermodynamically the more stable. With time, the concentration of the species hydrated in the 3,4-position reaches a maximum (about 64% of the total concentration). Thereafter, it falls steadily and the concentration of the 7,8-adduct rises until, at equilibrium, the latter accounts for 92% of the total and the 3,4-adduct for only 7.6%. In 2,6-dihydroxy-4-methylpteridine, the methyl group drastically reduces the extent of water addition to the 3,4-position but does not significantly affect 7,8-addition, so that, spectroscopically, only a first-order conversion of anhydrous molecule into the 7,8-water-adduct is observed.²⁹

VII. Reversible Ring Opening

In acid solution, pteridine rapidly adds a molecule of water to form "hydrated pteridine," 3,4-dihydro-4-hydroxypteridine. This cation slowly undergoes fission of the dihydropyrimidine ring to form the cation of 2-aminomethyleneamino-3-formylpyrazine (5). This ion is probably stabilized, at least partly, by amidinium-type resonance. On neutralization, ring-closure takes place slowly to give the equilibrium ratio of pteridine and "hydrated pteridine."² Similar behavior is shown by 2-, 4-, and 7-methylpteridine. The ring-opening reaction is acid catalyzed, the rate varying linearly with hydrogen ion activity.¹⁷ Constants for the reaction are summarized in Table IX.

On neutralization, the ring-opened species slowly ring-closes again. At 20°, for the ring-opened substance from pteridine, the first-order rate constant is about 10^{-4} sec^{-1} .¹⁷

6-Amino-³¹ and 6-chloro-pteridine³⁵ also give this reversible ring-opening reaction in acid solution.

TABLE IX
RATE CONSTANTS FOR THE RING-OPENING REACTION
OF HYDRATED CATIONS^{a, b}

Species	<i>a</i>	<i>b</i>	T, °C
Pteridine	1.00	0.458	12.5
Pteridine	3.00	1.24	20.3
Pteridine	10.8	3.03	30.5
2-Methylpteridine	0.90	2.22	20.1
4-Methylpteridine	35	56	14.4
4-Methylpteridine	90	173	20.2
7-Methylpteridine	11	13.0	19.9

^a Taken from Y. Inoue and D. D. Perrin, *J. Chem. Soc.* 2648 (1963).

^b Constants *a* and *b* are for the equation $10^4 k_{ro} = a + b(a_H^+)$, where k_{ro} is in sec⁻¹.

Although ring-opening also occurs in the hydrated cations of 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-triazanaphthalene, the reaction, which is much slower than the water-addition step, appears to be irreversible,²⁶ because decomposition of the ring-opened species supervenes.

Recent Advances in Oxazolone Chemistry

ROBERT FILLER

*Department of Chemistry,
Illinois Institute of Technology, Chicago, Illinois*

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I. Introduction and Nomenclature

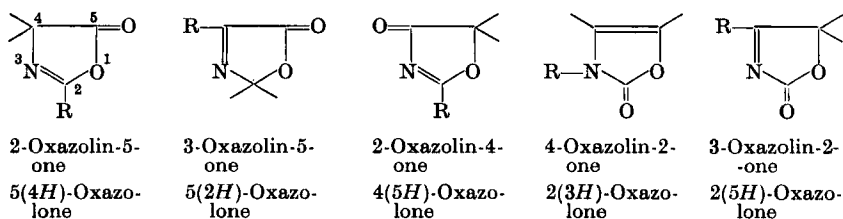
The last comprehensive review of the chemistry of oxazolones¹ covered the literature through 1954. Most of the studies up to that time stemmed from either interest in the role of azlactones as precursors of α -amino acids and peptides or the monumental studies on penicillin,² which, for a time, was thought to possess an oxazolone ring, rather than the correct β -lactam moiety.

Since about 1955, a considerable number of new developments of wide synthetic, structural, and mechanistic interest have been described. It is the purpose of this review to discuss the significant features of these new advances.

Five different structures may be written for the oxazolones. Their skeletal formulas, the *Chemical Abstracts'* nomenclature (listed first), and the names with more common usage follow.

¹ J. W. Cornforth, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. V, pp. 336-377. Wiley, New York, 1957.

² "The Chemistry of Penicillin" (H. T. Clarke, J. R. Johnson, and R. Robinson, eds.). Princeton Univ. Press, Princeton, N.J., 1949.



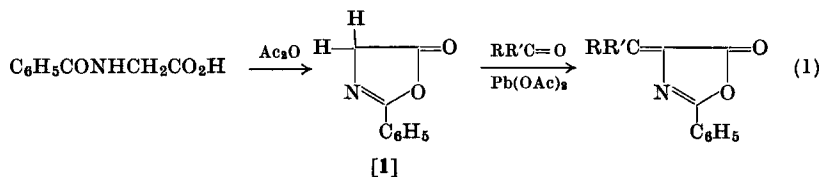
The 5(4*H*)-oxazolones are the familiar azlactones, and it is with this type that most studies have been conducted. The 5(2*H*)-oxazolones are frequently referred to as pseudooxazolones, and there has been an increasing interest in the behavior of these compounds. A number of studies of the 2(3*H*)-system have been reported recently, and the existence of the 4(5*H*)-system, previously in doubt, now seems firmly established. The 2(5*H*)-oxazolones, however, remain unknown.

II. 2-Oxazolin-5-ones

A. METHODS OF PREPARATION

1. General Methods

Several improved methods for the preparation of known unsaturated azlactones as well as some interesting new compounds of this type have been reported. Crawford and Little³ observed that the direct use of 2-phenyl-5-oxazolone (**1**) in the Erlenmeyer reaction gave much improved yields (35–74%) of unsaturated azlactones with aliphatic aldehydes and with ketones such as acetone and cyclohexanone [Eq. (1)]. The usual procedure of mixing a carbonyl compound, hippuric acid, acetic anhydride, and sodium (or lead) acetate affords poor yields⁴ in the aliphatic series.



Aromatic aldehydes react rapidly with hippuric acid in the presence of a sulfur trioxide–dimethylformamide complex⁵ to form azlactones

³ M. Crawford and W. T. Little, *J. Chem. Soc.* 729 (1959).

⁴ H. E. Carter, P. Handler, and D. B. Melville, *J. Biol. Chem.* **129**, 359 (1939).

⁵ E. Baltazzi and E. A. Davis, *Chem. Ind. (London)* 929 (1962).

in 60–98% yield. By this method, azlactones containing free aromatic hydroxyl groups may be prepared from phenolic aldehydes, such as salicylaldehyde and vanillin. Previously, only the acetoxy compounds could be isolated, although these may be deacetylated to the hydroxy analogs with cold concentrated sulfuric acid.⁶

The reaction of hippuric acid with a three-fold excess of trifluoroacetic anhydride gives a 90% yield of 2-phenyl-4-(2',2',2'-trifluoro-1'-hydroxyethylidene)-5-oxazolone (2).⁷ This compound is also obtained



in high yield by the interaction of $(\text{CF}_3\text{CO})_2\text{O}$ with 1. In contrast to the behavior in acetic anhydride,⁸ the latter reaction proceeds in the absence of a nitrogen base. This may be due to the greater electrophilic character of the carbonyl carbon in trifluoroacetic anhydride, as well as to a further increase in electrophilicity resulting from protonation by the trifluoroacetic acid formed during the reaction. Pyridine is necessary to form 2-phenyl-4-(1'-hydroxybenzylidene)-5-oxazolone from benzoic anhydride and sodium hippurate.⁹

The enolic form of 2 was confirmed by a ferric chloride color reaction and by its acidity and ultraviolet spectrum. *N*-Aroyl derivatives of amino acids other than glycine fail to form such azlactones, probably because the stabilization afforded by enolization cannot occur.

Compound 2 is hydrolyzed in boiling water to form the hydrate of benzamidotrifluoroacetone (3) with loss of carbon dioxide. This behavior is readily understood in terms of a facile decarboxylation of the initially formed β -keto acid.

A number of unusual aliphatic trifluoromethyl compounds have been obtained from 4-hexafluoroisopropylidene-2-phenyl-5-oxazolone (4).¹⁰ The latter was prepared as shown in Eq. (2). The ease of formation

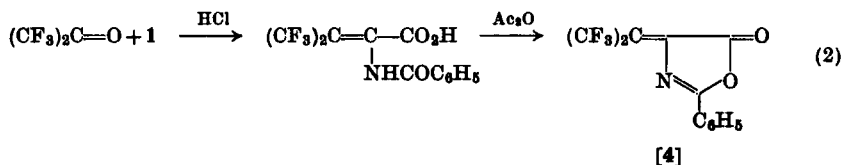
⁶ V. N. Gupta, *J. Sci. Ind. Res. (India)* **19B**, 117 (1960).

⁷ E. J. Bourne, J. Burdon, V. C. R. McLoughlin, and J. C. Tatlow, *J. Chem. Soc.* 1771 (1961).

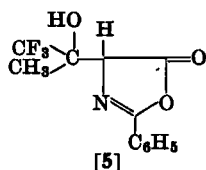
⁸ J. Attenburrow, D. F. Elliott, and G. F. Penny, *J. Chem. Soc.* 310 (1948).

⁹ British Patent 720,649 (1954); *Chem. Abstr.* **50**, 1922 (1956).

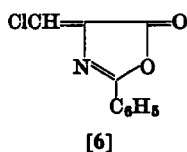
¹⁰ E. M. Rokhlin, N. P. Gambaryan, Ch'ng-Yün Ch'eng, and I. L. Knunyants, *Dokl. Akad. Nauk SSSR* **134**, 1367 (1960).



of the unsaturated compound is somewhat surprising in view of the known resistance of such highly fluorinated compounds to dehydration. This is borne out by the observation¹¹ that trifluoroacetone and hippuric acid give a mixture of diastereomers of the saturated azlactone **5** in acetic anhydride-acetate medium.



A new synthesis of unsaturated azlactones, which is especially useful in cases where the aldehyde is not readily available, has been developed.¹² The reaction involves the nucleophilic displacement of chlorine in 4-chloromethylene-2-phenyl-5(4*H*)-oxazolone (**6**)¹³ by a



hydrogen compound, usually activated by formation of an organo-metallic reagent. The extreme lability of the chloro group is consistent with its vinylogous acid halide structure. The method is illustrated in Eqs. (3) and (4).

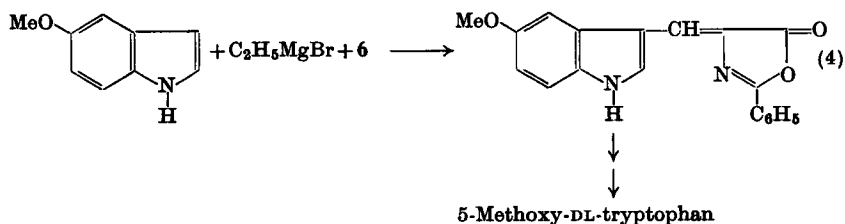
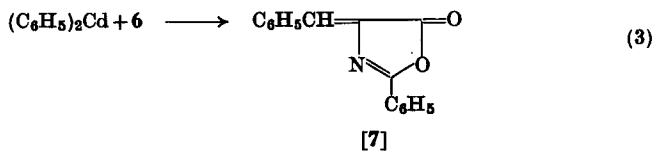
Pyrrole gives one 2-pyrrolydene isomer, but without activation a mixture of geometric isomers¹⁴ is isolated.

¹¹ Dr. J. Burdon, Univ. of Birmingham, England, private communication (1963).

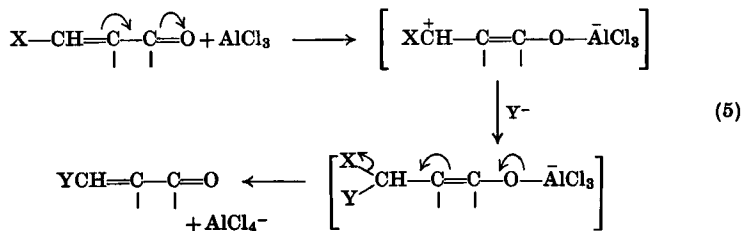
¹² H. Behringer and H. Taul, *Chem. Ber.* **90**, 1398 (1957).

¹³ This compound is prepared from ethyl orthoformate and hippuric acid by a convenient three-step procedure, *cf.* ref. 1.

¹⁴ W. Herz, *J. Am. Chem. Soc.* **71**, 233 (1949).



The behavior of such activated halides as alkylating agents under Friedel-Crafts conditions expands the scope of the synthesis. Aluminum chloride enhances the electrophilic character of the α,β -unsaturated carbonyl system and permits the nucleophilic attachment of the aromatic addendum (Y^-) to the carbon bearing the positive charge, with displacement of halogen [Eq. (5)]. Thus,

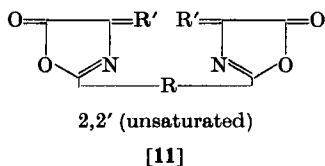
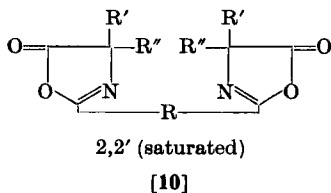
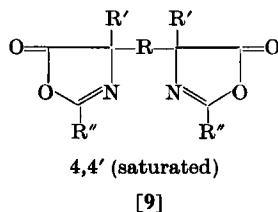
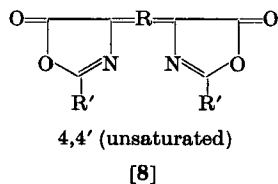


benzene and compound 6 react in the presence of anhydrous aluminum chloride to give 7. Chlorobenzene, fluorobenzene, diphenyl ether, and dimethylaniline behave similarly to give *p*-substituted arylidene products in uniformly high yields (93–97%).

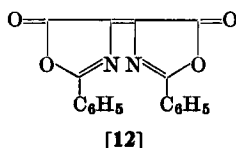
2. Bis-oxazolones

There are four possible classes of bis-5(4*H*)-oxazolones (cf. 8–11). Compounds of type 8 may be prepared by the Erlenmeyer reaction on dialdehydes. The compound in which R is derived from the 4,4'-dialdehyde of diphenyl ether ($R' = C_6H_5$) is a recent example.¹⁵

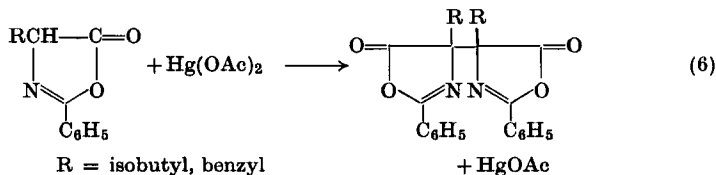
¹⁵ E. Guštak and A. Markovac-Prpić, *Arkiv Kemi* **27**, 125 (1955).



"Hippuroflavin,"¹⁶ formed by action of PCl_5 on ethyl hippurate, is believed to be the bis-oxazolone **12**.¹⁷



Compounds with structure **9** have been obtained by oxidative coupling of 4-alkyloxazolones,¹⁸ using mercuric acetate, as shown in Eq. (6). The structure was deduced from molecular weight data,



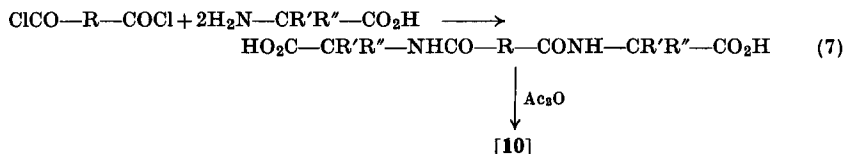
ultraviolet spectra, and the observation that 2-benzyl-4,4-dimethyl-oxazolone was not significantly oxidized. Although compound **1** was readily attacked by oxidizing reagents, no pure product could be isolated.

¹⁶ L. Rügheimer, *Ann. Chem.* **287**, 50 (1895).

¹⁷ Ref. 2, p. 771.

¹⁸ Ref. 2, pp. 738, 792.

The saturated 2,2'-bis-oxazolones (**10**) are conveniently prepared [Eq. (7)] in two-steps *via* *N,N'*-diacylbis-(α -amino acids), which cyclize in hot acetic anhydride.^{19, 20} If R is aliphatic, alkali hydroxides are used in the Schotten-Baumann reaction, whereas magnesium



oxide is preferred when R is aromatic. The cyclization conditions are critical, to minimize the Dakin-West reaction,²¹ when α -hydrogens are present in the amino acid.

The reactions of these useful difunctional compounds are discussed in Section II, B, 4.

There are no reported examples of unsaturated 2,2'-bis-oxazolones (**11**), although it is likely that they could be prepared from aldehydes and *N,N'*-diacylbis-glycines.

B. REACTIONS

1. Azidolysis

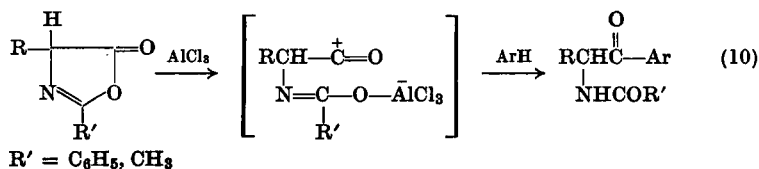
Both saturated and unsaturated 5(4*H*)-oxazolones behave as cyclic *O*-acylimino ethers on reaction with hydrazoic acid giving substituted tetrazolecarboxylic acids²² by *alkyl cleavage* and cyclization of the unstable imidazide. There is no evidence for the presence of acid azide amides, the products of the alternate *acyl* ring fission. Thus, compound **13** is converted in nearly quantitative yield into α -(5-methyl-1-tetrazolyl)cinnamic acid (**14**), as indicated in Eq. (8). The reaction proceeds much more slowly when the 2-methyl group is replaced by an aryl group. The structure of **14** was established by epoxidation and periodate cleavage to form benzaldehyde, 5-methyltetrazole, and oxalic acid. In similar fashion, 4-benzyl-2-methyl-5-oxazolone (**15**) is converted into the corresponding substituted β -phenylpropionic acid; the latter is also obtained by hydrogenation of **14**.

¹⁹ C. S. Cleaver and B. C. Pratt, *J. Am. Chem. Soc.* **77**, 1544 (1955).

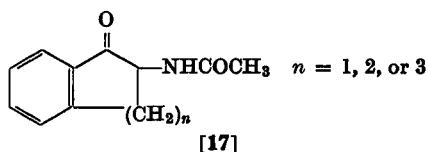
²⁰ T. M. Frunze, V. V. Korshak, and L. V. Kozlov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 535 (1959).

²¹ H. D. Dakin and R. West, *J. Biol. Chem.* **78**, 91, 757 (1928).

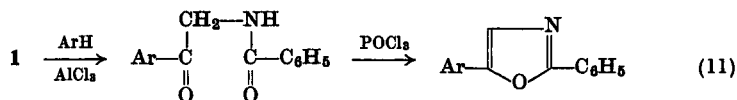
²² H. Behringer and W. Grimme, *Chem. Ber.* **92**, 2967 (1959).



is benzene, toluene, or anisole. When R is benzyl, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2$, or $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2$ these intermolecular reactions are accompanied by



intramolecular acylation to form cyclic acylamino ketones (17).²⁵ The open-chain acylamino ketones may be cyclized in 85–95% yields, and this is a good synthetic route [Eq. (11)] to 2,5-diaryloxazoles.^{26, 27}



In contrast to the saturated azlactones, the Friedel-Crafts reaction of 2-substituted-4-arylidene-5-oxazolones is quite complex and may follow several different courses, often concurrently, depending on both reaction conditions and structural variations in the arylidene ring. This behavior is readily interpreted in terms of the α,β -unsaturated carbonyl moiety and the cross-conjugated system containing nitrogen, both of which provide potential reaction sites in addition to the lactone carbonyl group. The reaction has been investigated^{28–32}

²⁵ E. Ciorănescu, and L. Birlădeanu, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **149** (1961).

²⁶ P. T. Frangopol, A. T. Balaban, L. Birlădeanu, and E. Ciorănescu, *Tetrahedron* **16**, 59 (1961).

²⁷ A. T. Balaban, I. Bally, P. T. Frangopol, M. Băcescu, E. Ciorănescu, and L. Birlădeanu, *Tetrahedron* **19**, 169 (1963).

²⁸ R. Filler and L. M. Hebron, *J. Org. Chem.* **23**, 1815 (1958).

²⁹ R. Filler and Y. S. Rao, *J. Org. Chem.* **27**, 2403 (1962).

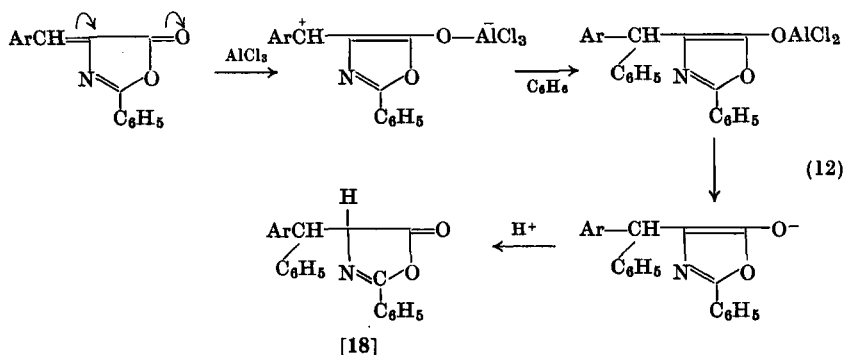
³⁰ W. I. Awad and M. S. Hafez, *J. Org. Chem.* **26**, 2055 (1961).

³¹ E. Ciorănescu, L. Birlădeanu, A. T. Balaban, and C. D. Nenitzescu, *Tetrahedron Letters* **349**, 887 (1962).

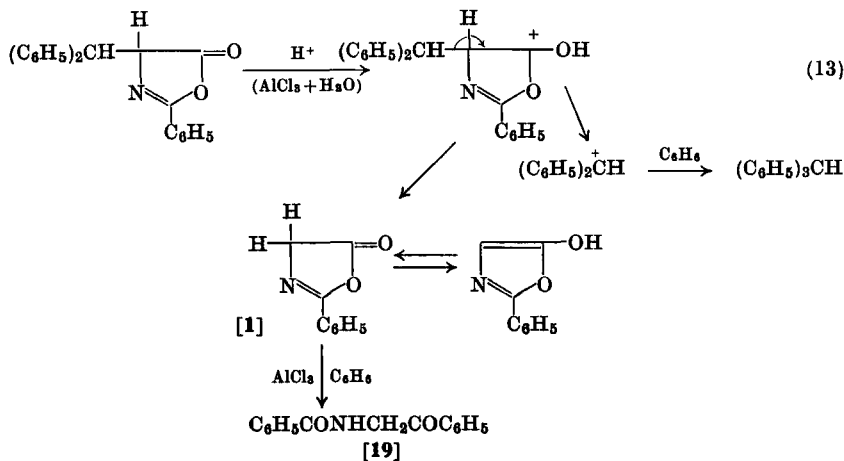
³² R. Filler and Y. S. Rao, *J. Heterocyclic Chem.*, in press.

in considerable detail and the following conclusions have been drawn:

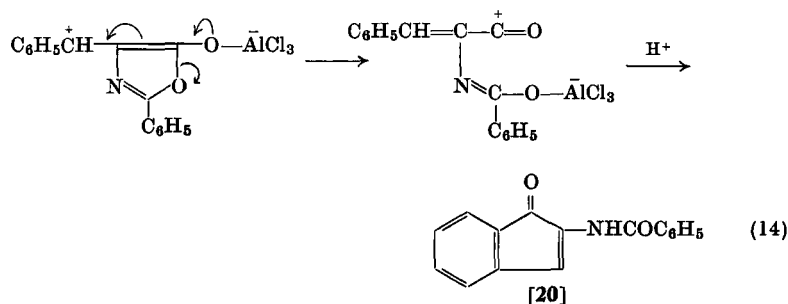
(1) In benzene, toluene, chlorobenzene, and anisole, the products reflect participation of the solvent as a reactant, whereas in inert solvents two types of products, formed by *intramolecular* processes, are isolated.



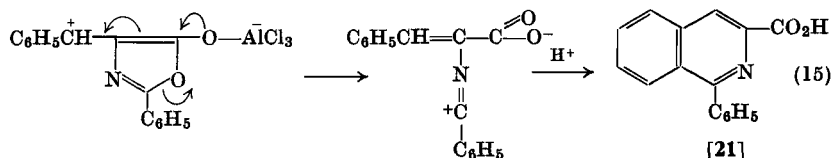
(2) In the presence of freshly sublimed aluminum chloride and under anhydrous conditions, compounds such as **7** react with benzene to form 1,4-addition products, the saturated azlactones **18**, in 70–75% yield^{28, 29, 31} [Eq. (12)]. If moisture is not excluded, fragmentation of the saturated azlactone occurs to give, after acylation, ω -benzamidoacetophenone (**19**) and triphenylmethane [Eq. (13)].^{29, 30, 31}



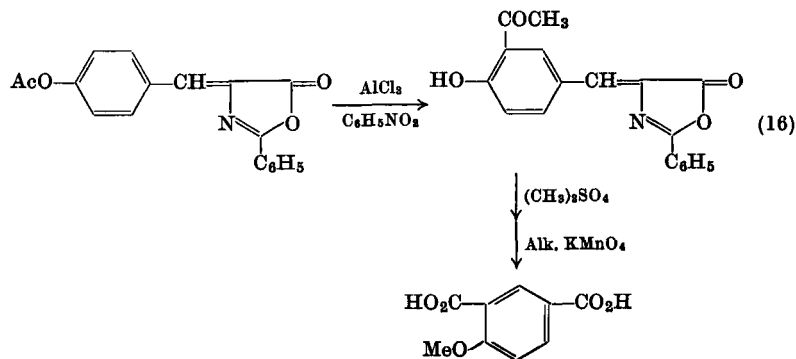
(3) The nature and position of substituents on the aryldiene ring markedly affect the ratio of addition products to cleavage products. As expected, electron-releasing substituents enhance the cleavage reaction.



(4) With tetrachloroethane as solvent, two modes of ring-opening occur, leading to the formation of 2-benzamidoindenone (20), by *intramolecular acylation*^{29, 30} [Eq. (14)], and 1-phenylisoquinoline-3-carboxylic acid²⁹ (21), by intramolecular *imidoylation* [Eq. (15)].

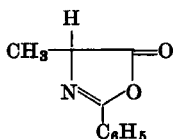


(5) There is usually no reaction with nitrobenzene as solvent. However, in this medium acetoxybenzylidene azlactones undergo a Fries rearrangement³² [Eq. (16)].

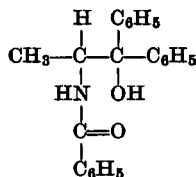


3. Reactions with Grignard Reagents

4-Methyl-2-phenyl-5-oxazolone (**22**) reacts with excess phenylmagnesium bromide to give 2-benzamido-1,1-diphenyl-1-propanol¹⁸ (**23**). With excess ethylmagnesium bromide, **22** forms a dimer, *N,N'*-

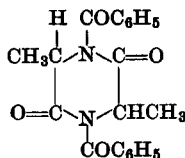


[22]

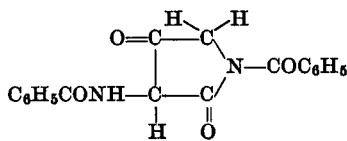


[23]

dibenzoyl-3,6-dimethyl-2,5-diketopiperazine³³ (**24**). Compound **1**, however, is converted into a complex mixture³⁴ from which the dimeric acid, 3-benzamido-1-benzoylpyrrolidine-2,4-dione (**25**), has been isolated.



[24]



[25]

The behavior of unsaturated azlactones with organometallic reagents has been studied in detail.³⁵⁻⁴³ Arylmagnesium halides and phenyllithium attack 4-arylidene-5-oxazolones at the carbonyl carbon to give ring-opened amido tertiary alcohols (**26**) and oxazolines (**27**) (by ring closure), usually as mixtures³⁵⁻³⁹ [Eq. (17)]. The nature of the Grignard reagent³⁹ and dilution factors³⁷ determine the ratio of the

³³ Ref. 2, pp. 768-9.

³⁴ Ref. 2, pp. 738, 845-6.

³⁵ H. Pourrat, *Bull. Soc. Chim. France* 828 (1955).

³⁶ A. Mustafa and A. H. E. Harhash, *J. Org. Chem.* **21**, 575 (1956).

³⁷ R. Filler and J. D. Wismar, *J. Org. Chem.* **22**, 853 (1957).

³⁸ W. I. Awad and M. S. Hafez, *J. Org. Chem.* **25**, 1180 (1960).

³⁹ W. I. Awad and M. S. Hafez, *J. Org. Chem.* **25**, 1183 (1960).

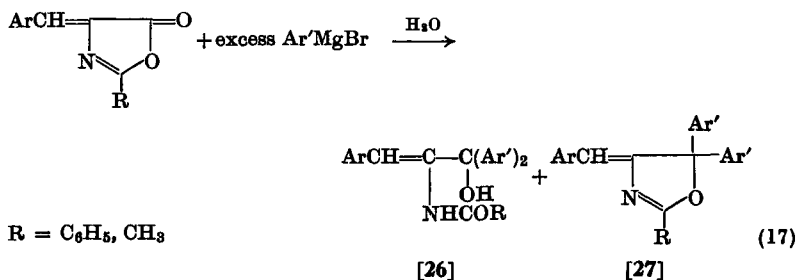
⁴⁰ L. Horner and H. Schwahn, *Ann. Chem.* **591**, 99 (1955).

⁴¹ R. Filler, K. B. Rao, and Y. S. Rao, *J. Org. Chem.* **27**, 1110 (1962).

⁴² R. Filler and Y. S. Rao, *J. Org. Chem.* **27**, 3348 (1962).

⁴³ W. Asker and Z. E. Elagroudi, *J. Org. Chem.* **26**, 1440 (1961).

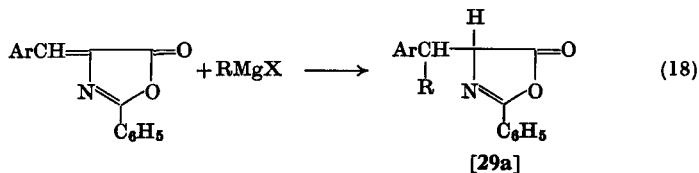
products, and in some cases one product is formed exclusively.³⁹ The alcohols cyclize to the oxazolines with acetic anhydride^{37, 38} and to substituted indenenes³⁸ (28) with hydrochloric acid-acetic acid.



When compound 7 is treated in a 1:1 ratio with phenylmagnesium bromide using inverse addition,³⁷ the reaction is sluggish and stops at the ketone stage giving α -benzamido benzalacetophenone (29) in low yield as the only isolable product.

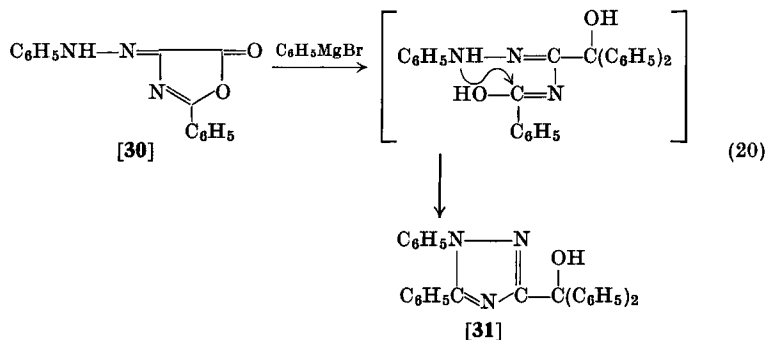


In contrast to these ring-opening reactions, it was observed by Horner and Schwahn⁴⁰ that 4-arylidene-(isopropylidene and cyclohexylidene)-oxazolones react with *alkyl* Grignard reagents by conjugate addition to give saturated azlactones 29a as the only products [Eq. (18)].



Filler *et al.*⁴¹ noted that the labile geometric isomer of 7 gives saturated azlactones (18) in 35–40% yields, as well as products of 1,2-addition, when treated with several arylmagnesium bromides. This stereoselectivity appears to be the only reported difference in chemical behavior between isomers of this type.

4-Arylazo-2-phenyl-5-oxazolone (**30**) is converted into the 1,2,4-triazole **31** by the action of phenylmagnesium bromide⁴³ [Eq. (20)].



4. Amino Acid and Peptide Syntheses

Saturated azlactones such as **18** and **29a**, whose preparation is discussed in parts 2, b and 3 of this section, are useful intermediates for the synthesis of a variety of β,β -disubstituted alanines (**32**).^{40, 46}

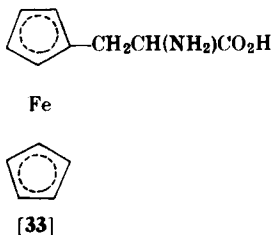


R = alkyl or aryl

[32]

The azlactones are first hydrolyzed with alkali to the *N*-benzoylamino acid and thence to **32** using an HBr-acetic acid mixture.

A number of new β -substituted alanines have been prepared from unsaturated azlactones by the usual reduction-hydrolysis procedures. An interesting example is the synthesis of DL- β -ferrocenylalanine (**33**).^{47, 48}



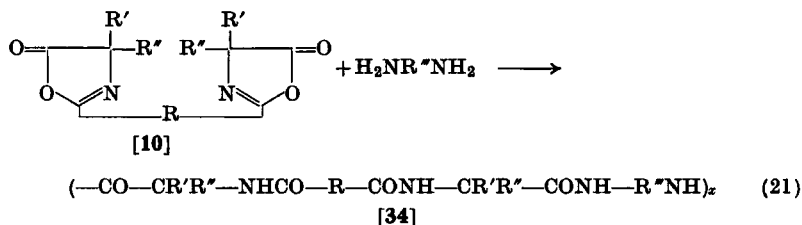
⁴⁶ R. Filler and Y. S. Rao, *J. Org. Chem.* **26**, 1685 (1961).

⁴⁷ K. Schlögl, *Monatsh. Chem.* **88**, 601 (1957).

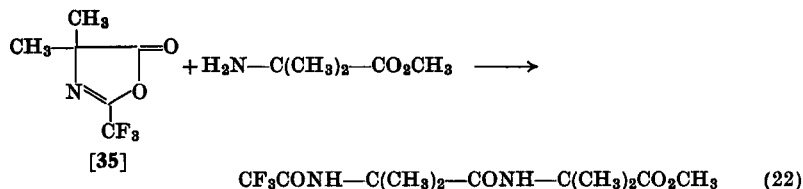
⁴⁸ J. M. Osgerby and P. L. Pauson, *J. Chem. Soc.* 656 (1958).

The synthesis of γ -hydroxyvaline and γ,γ' -dihydroxyvaline *via* azlactones has been reported recently.⁴⁹

Saturated 2,2'-bis-5-oxazolones (**10**) react with diamines under mild conditions to form polyamides (**34**) of high molecular weight in quantitative yield [Eq. (21)].⁵⁰ These polymers are composed of dicarboxylic acid, α -amino acid, and diamine units in a regular arrangement of both "head-to-tail" and "tail-to-tail" amide groups. They represent a "cross" between conventional polyamides and α -amino acid homopolymers. A feature of this polymerization is that no small molecules such as H_2O , NH_3 , or CO_2 are lost during reaction.



Difficulties are often encountered in the formation of peptides from α -amino acids which lack an α -hydrogen atom, e.g. α -methylalanine, presumably because of steric hindrance. This problem is obviated by use of the oxazolone **35**, an excellent reagent for the addition of a single α -methylalanyl residue to an amine or amino acid [Eq. (22)]⁵¹



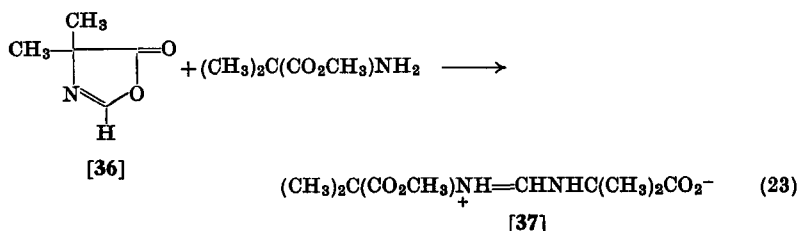
(see also Section III, B). Both trifluoroacetyl amino and ester groups are hydrolyzed by alkali to give the dipeptide. The alkaline hydrolysate may be converted into the carbobenzyloxy dipeptide, which forms a new oxazolone on dehydration. The latter reacts with the amino acid ester to give the protected tripeptide.

⁴⁹ E. Galantay, A. Szabo, and J. Fried, *J. Org. Chem.* **28**, 98 (1963).

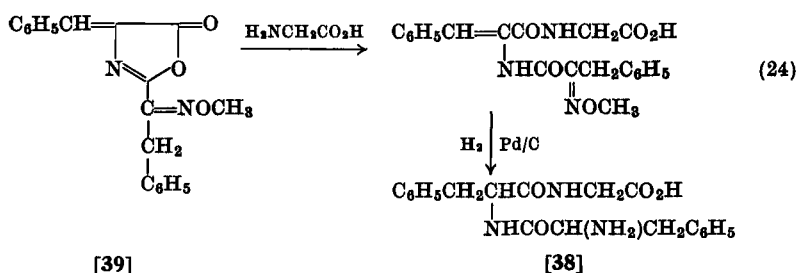
⁵⁰ C. S. Cleaver and B. C. Pratt, *J. Am. Chem. Soc.* **77**, 1541 (1955).

⁵¹ M. T. Leplawy, D. S. Jones, G. W. Kenner, and R. C. Sheppard, *Tetrahedron* **11**, 39 (1960).

The rather unstable 4,4-dimethyloxazolone **36** fails to behave in this manner, but yields instead the amidine **37** by attack of the amino compound at the methine linkage [Eq. (23)].



An interesting new synthesis [Eq. (24)] of the tripeptide DL-phenylalanylphenylalanylglycine (**38**) from the oxazolone **39** has been reported.⁵²



5. Conversion into Other Nitrogen Heterocycles

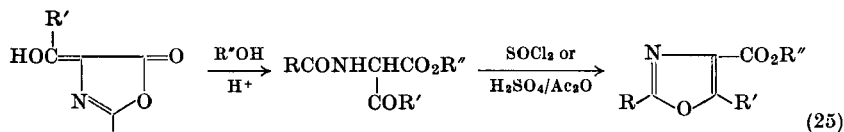
The 4-unsaturated-5-oxazolones provide convenient starting materials for the synthesis of other nitrogen-containing heterocyclic systems. The preparation of tetrazoles and isoquinolines is discussed in Sections II, B, 1 and II, B, 2, b.

The hetero ring in 4-(1'-hydroxyalkylidene)-5-oxazolones is cleaved by alcoholic HCl to form alkyl α -acylaminoacylacetates, which cyclize to oxazole-4-carboxylates⁵³ [Eq. (25)]. This rearrangement occurs directly in alkali, and a carbon-14 tracer study has substantiated a mechanism involving ring opening followed by the alternative ring closure.⁵⁴

⁵² L. M. C. Shen and W. H. Hartung, *J. Org. Chem.* **23**, 96 (1958).

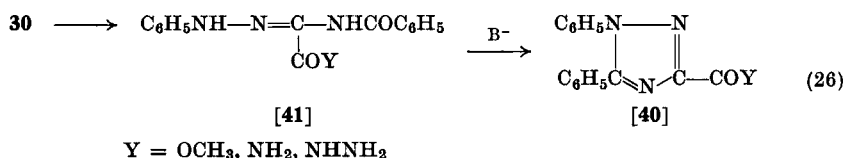
⁵³ F. Korte and K. Storiko, *Chem. Ber.* **93**, 1033 (1960).

⁵⁴ C. G. Stuckwisch and D. D. Powers, *J. Org. Chem.* **25**, 1819 (1960).

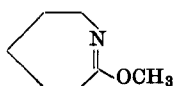


R = C₆H₅; R' = H, CH₃

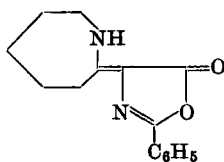
The conversion of a 4-aryldio-5-oxazolone into a 1,2,4-triazole by reaction with a Grignard reagent is mentioned in Section II, B, 3.⁴³ In similar fashion, the rearrangement of compound **30** to derivatives of 3-carboxy-1,5-diphenyl-1*H*-1,2,4-triazoles (**40**) proceeds readily in the presence of strong nucleophiles [Eq. (26)].^{55, 56} This transformation undoubtedly occurs by ring opening and dehydrative cyclization, and, indeed, the acyclic amide and hydrazide **41** have been isolated.⁵⁶



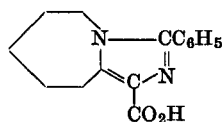
The oxazolone **43**, prepared by reaction of *O*-methylcaprolactim (**42**) with compound **1**, undergoes a ring-opening reaction with methanolic HCl and cyclizes in alkaline medium to 1,5-pentamethylene-2-phenylimidazole-4-carboxylic acid (**44**),⁵⁷ which can be decarboxylated easily.



[42]



[43]



[44]

6. Miscellaneous Reactions

When 4-benzylidene-2-methyl-5-oxazolone (**45**) is prepared by the Erlenmeyer procedure, a light yellow product is generally isolated. Rüfenacht⁵⁸ showed that pure **45** is white and that the colored

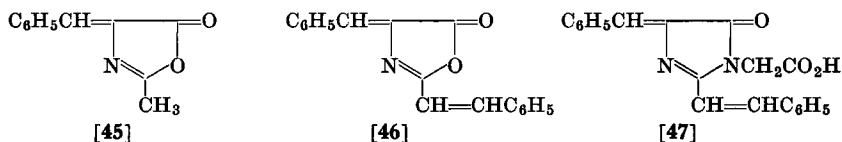
⁵⁵ G. W. Sawdey, *J. Am. Chem. Soc.* **79**, 1955 (1957).

⁵⁶ E. J. Browne and J. B. Polya, *Chem. Ind. (London)* 1086 (1960); *J. Chem. Soc.* 575 (1962).

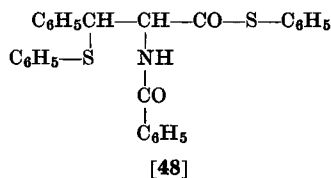
⁵⁷ R. G. Glushkov and O. Yu. Magidson, *Zh. Obshch. Khim.* **30**, 1855 (1960).

⁵⁸ K. Rüfenacht, *Helv. Chim. Acta* **37**, 1451 (1954).

contaminant is 4-benzylidene-2-styryl-5-oxazolone (**46**), formed by further condensation of the active methyl group of **45** with excess benzaldehyde. Bergmann *et al.*⁵⁹ previously had reported a second by-product, which has been shown by Pfeleger and Pelz⁶⁰ to be 4-benzylidene-1-carboxymethyl-2-styryl-5-imidazolone (**47**). The



structure of this compound was established by identification of fragments arising from acid hydrolysis of the product obtained on complete hydrogenation of **47**.



4-Arylidene-5-oxazolones undergo a ring-opening reaction with aromatic thiols and a second mole of thiol is then incorporated to give products such as **48**.⁶¹



The chlorination of **45** in an acetic acid-acetic anhydride mixture leads to a pentachloro-acetoxy compound (**49**),⁶² but in acetic

⁵⁹ J. E. Tietzman, D. G. Doherty, and M. Bergmann, *J. Biol. Chem.* **151**, 393 (1943).

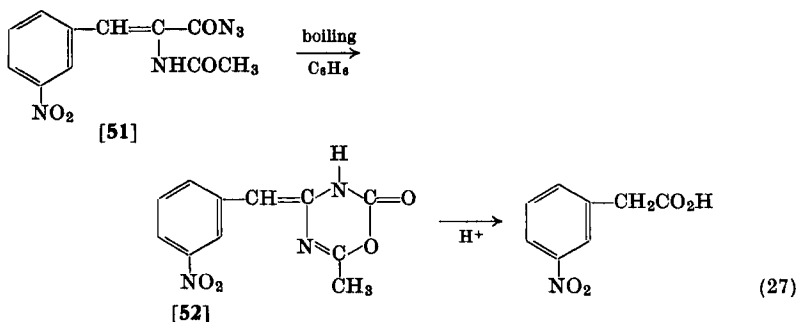
⁶⁰ R. Pfeleger and J. Pelz, *Chem. Ber.* **90**, 1489 (1957).

⁶¹ A. Mustafa, A. H. E. Harhash, and M. Kamel, *J. Am. Chem. Soc.* **77**, 3860 (1955).

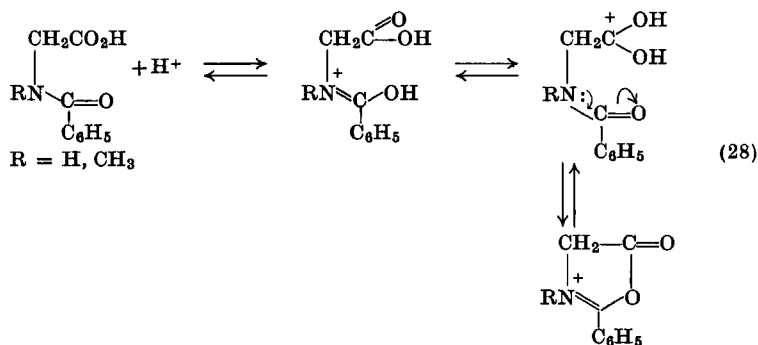
⁶² R. Pfeleger and A. Sauter, *Chem. Ber.* **90**, 1475 (1957).

anhydride only, or in carbon tetrachloride, the dichloro analog **50** is obtained.⁶³ The corresponding dibromo compound is isolated in any of these media.

Compound **7** is reduced to 2-benzamidocinnamyl alcohol by calcium borohydride in hydroxylic solvents at low temperatures.⁶⁴ This reduction had been accomplished previously⁶⁵ using lithium aluminum hydride in tetrahydrofuran.



A useful reaction sequence has been developed for conversion of an aromatic aldehyde into the next higher homologous acid.⁶⁶ The nitro analog of **45**, prepared from *m*-nitrobenzaldehyde, is converted into the azide **51** by hydrazinolysis and treatment with nitrous acid. The



azide forms the substituted 2-oxo-1,3,5-oxadiazine **52**, presumably *via* the isocyanate, and **52** gives *m*-nitrophenylacetic acid on treatment with acid [Eq. (27)].

Cryoscopic studies have shown that α -acylamino acids undergo

⁶³ R. Pflieger and G. Markert, *Chem. Ber.* **90**, 1482 (1957).

⁶⁴ J. Kollonitsch, O. Fuchs, and V. Gabor, *Nature* **175**, 348 (1955).

⁶⁵ E. Baltazzi and R. Robinson, *Chem. Ind. (London)* 540 (1953).

⁶⁶ K. F. Jennings, *J. Chem. Soc.* 1512 (1957).

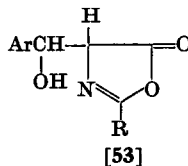
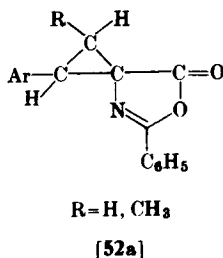
complex ionization in 100% sulfuric acid to form oxazonium ions [Eq. (28)].⁶⁷ Furthermore, azlactonization of these acids in acetic anhydride is catalyzed by sulfuric acid.

It has been shown recently^{67a} that 4-arylidene-2-phenyl-5-oxazolones react with diazoalkanes at the exocyclic double bond to give compounds of type **52a**. The proton magnetic resonance spectra of these compounds support the cyclopropyl structure.

C. STEREOCHEMISTRY

1. Geometric Isomerism

The isolation of several pairs of geometric isomers of 4-unsaturated-5-oxazolones has been described.⁶⁷⁻⁷¹ Generally, only one isomer is obtained when an aldehyde reacts with hippuric acid in the presence of acetic anhydride. Occasionally, mixtures have been separated in base-catalyzed reactions.⁶⁹⁻⁷¹ In acetic anhydride-sulfuric acid or in 100% sulfuric acid, a mixture is obtained, and it has been suggested⁶⁷ that sulfuric acid inhibits mutarotation of the intermediate addition product **53**, which is a mixture of diastereomers (see, e.g., compound



5 and Section II, A, 1). The *threo* pair, by *trans* elimination, would afford one geometric isomer and the *erythro* pair the other isomer. In the absence of mutarotation and assuming equal rates of elimination, the overall reaction should yield an equimolar mixture of isomers. It has been demonstrated⁶⁷ that mixtures are not formed by isomerization of unsaturated azlactones in these media. Independent evidence that sulfuric acid can inhibit mutarotation is found in polarimetric studies on the rate of racemization of *N*-benzoyl-D-alanine.⁶⁷ In acetic anhydride racemization is complete within ten hours at room temperature, whereas in 100% sulfuric acid only one-third of the rotatory

⁶⁷ J. L. O'Brien and C. Niemann, *J. Am. Chem. Soc.* **79**, 80 (1957).

^{67a} W. I. Awad, A. K. Fateen, and M. A. Zayed, *Tetrahedron* **20**, 891 (1964).

⁶⁸ H. E. Carter and W. C. Risser, *J. Biol. Chem.* **139**, 255 (1941).

⁶⁹ W. Herz, *J. Am. Chem. Soc.* **71**, 3982 (1949).

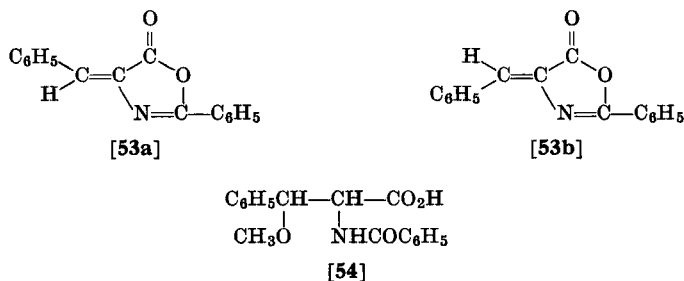
⁷⁰ J. P. Lambooy, *J. Am. Chem. Soc.* **76**, 133 (1954).

⁷¹ S. Larsen and J. Bernstein, *J. Am. Chem. Soc.* **72**, 4447 (1950).

power is lost after one week. Hence, sulfuric acid inhibits racemization of an optically active azlactone.

The preparation of the less stable isomer (**53b**) of the oxazolone **53a** involves a rather tedious procedure.^{68, 72} It has been reported^{41, 73} that **53a** is rapidly isomerized to **53b** in 48% hydrobromic acid saturated with gaseous HBr. In this way four azlactones have been converted into their isomers.⁴¹ It has been established, moreover, that the isomerization is radical-initiated and does not involve a carbonium ion intermediate.⁷⁴ The isomerization can be reversed by pyridine.⁶⁸

Attempts to establish the relative configurations of such pairs of isomers have been the subject of several investigations.^{49, 69, 72, 75, 76} Buckles *et al.*⁷² suggested tentative structural assignments for **53a** and **53b** and their respective benzamido acids on the basis of ultraviolet spectral data and by comparison of physical properties with those of model compounds. They pointed out that it is not possible to establish structural relationships from configurations of the diastereomeric 2-benzamido-3-methoxy-3-phenylpropionic acids (**54**), each of which, on treatment with acetic anhydride, give mixtures of the azlactones. Similar observations have been made by others.^{67, 68}



If mutarotation were not a factor, the *threo* pair would give the isomer having the phenyl group and nitrogen atom in a *cis* relationship and the *erythro* pair the isomer with the phenyl and carbonyl groups *cis*. Since it is doubtful, at least in some cases, that steric integrity is maintained in acetic anhydride prior to elimination, the subsequent

⁷² R. E. Buckles, R. Filler, and L. Hilfman, *J. Org. Chem.* **17**, 233 (1952).

⁷³ S. Tatsuoko and A. Morimoto, *Yakugaku Zasshi* **70**, 2531 (1950).

⁷⁴ R. Filler and Y. S. Rao, unpublished results (1963).

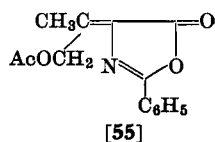
⁷⁵ G. Stefanovic and M. Stefanovic, *J. Org. Chem.* **21**, 161 (1956).

⁷⁶ N. K. Kochetkov, E. I. Budovski, R. M. Khomutov, M. Ya. Karpeiskii, and E. S. Severin, *Zh. Obshch. Khim.* **30**, 2573 (1960).

efforts^{75, 76} to relate the configurations of **53a** and **53b** to those of other *threo*- and *erythro*-diastereomers must necessarily be regarded with extreme caution.

On the basis of such eliminations and the acid strengths of the corresponding unsaturated hydroxamic acids, Kochetkov *et al.*⁷⁶ concluded that the structures of **53a** and **53b** are opposite to those shown.

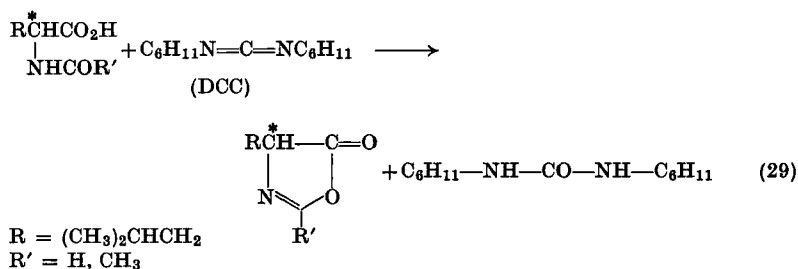
In favorable cases, cyclization reactions may be useful in establishing configurations,⁶⁹ but these methods may also be complicated by isomerizations. It is clear that other approaches are necessary to resolve this structural question. This has been accomplished⁴⁹ recently for the isomers of a related system (**55**) using proton magnetic resonance spectroscopy.



2. Optically Active Azlactones

It is mentioned in Section II, C, 1 that *N*-benzoyl-D-alanine cyclizes in 100% sulfuric acid to give an azlactone which racemizes very slowly.⁶⁷

A recent report⁷⁷ describes the conversion of *N*-formyl- and *N*-acetyl-L-leucine into optically active azlactones with dicyclohexylcarbodiimide (DCC) [Eq. (29)]. Other cyclization reagents, e.g. acetic anhydride, POCl₃, SOCl₂, and polyphosphoric acid, cause racemization. These azlactones react with optically active amino acid esters to give esters of dipeptides with retention of activity.



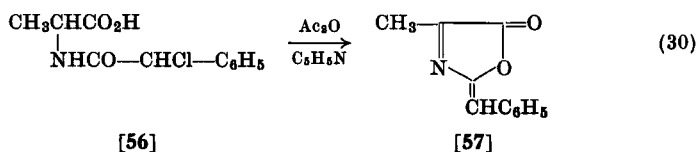
⁷⁷ I. Z. Siemion and K. Nowak, *Roczniki Chem.* **35**, 979 (1961).

III. 3-Oxazolin-5-ones

In recent years, several interesting developments in the chemistry of pseudooxazolones have been reported. The chemical properties of this system depend to some extent on the type of substitution at the 2-position of the hetero ring. The discussion, therefore, is divided into two parts.

A. 2-ARYLIDENEPSEUDOOXAZOLONES

The member of this class which has been studied most thoroughly is 2-benzylidene-4-methyl-5(2*H*)-oxazolone (**57**). This compound may be prepared by ring closure of either 3-bromo-2-phenylacetamidopropionic acid⁷⁸ or *N*-(α -halophenylacetyl)alanine (**56**)⁷⁹ [Eq. (30)]. These reactions presumably proceed *via* unstable halogeno-5(4*H*)-oxazolones,⁸⁰ which rapidly lose hydrogen halide.



A variety of melting points have been reported for **57**.^{78, 79, 81} Although the presence of geometric isomers has been suggested⁸² to explain these discrepancies, there is as yet no evidence to support this proposal. At least a partial explanation is to be found in the observation⁸³ that **57** undergoes photodimerization slowly in ordinary light and more rapidly when exposed to ultraviolet radiation. The monomer and dimer can be separated by vacuum sublimation. Infrared, ultraviolet, and proton magnetic resonance spectra of the dimer support the cyclobutane structure **58**, although the stereochemistry has not been definitely established.

While the possibility of a rapid equilibrium between the 5(2*H*)- and 5(4*H*)-isomers in compounds such as **57** exists, Knunyants *et al.*⁸⁴

⁷⁸ I. L. Knunyants and V. V. Shokina, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (English Transl.)* 409 (1955).

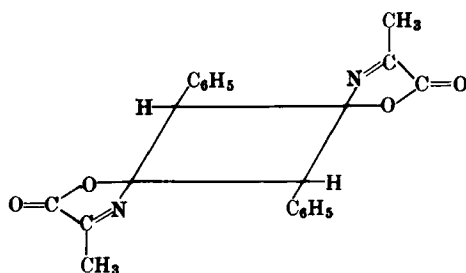
⁷⁹ J. A. King and F. H. McMillan, *J. Am. Chem. Soc.* **72**, 833 (1950).

⁸⁰ M. Bergmann and F. Stern, *Ann. Chem.* **448**, 20 (1926).

⁸¹ M. Brenner and K. Rüfenacht, *Helv. Chim. Acta* **37**, 203 (1954).

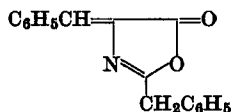
⁸² *Cf. ref. 1*, p. 375.

⁸³ R. Filler and E. J. Piasek, *J. Org. Chem.* **28**, 221 (1963).



[58]

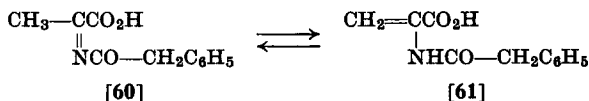
concluded that the preferred structure is the one which permits the most extended conjugation. Ultraviolet spectral evidence⁸⁵ favors the 5(2*H*) structure for **57**. In this connection it is interesting to note that only the cross-conjugated 5(4*H*)-oxazolone **59** is formed⁸⁶ by either the conventional Erlenmeyer route or the method illustrated in Eq. (30).



[59]

Both the 4- and 5-positions of the pseudooxazolones are susceptible to nucleophilic attack. The reactivity of the $>\text{C}=\text{N}-$ linkage is manifested by two types of behavior.

(a) *Bond rupture* under hydrolytic conditions. Compound **57** forms pyruvic acid and phenylacetamide in alkaline or neutral media and phenylacetic acid in dilute acid.⁸⁶ The precursor of these products is undoubtedly the imido acid **60**, which probably exhibits triad prototropy with 2-phenylacetamidoacrylic acid (**61**). In dilute sodium

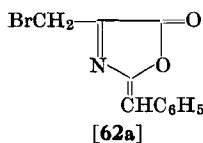
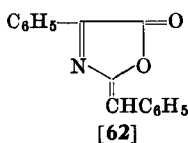


⁸⁴ O. V. Kil'disheva, M. G. Lin'kova, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 719 (1957).

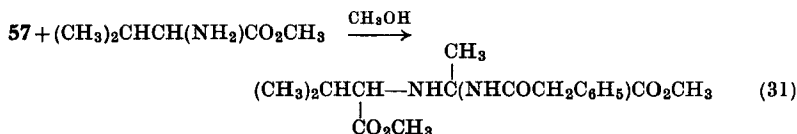
⁸⁵ Ref. 2, p. 795.

⁸⁶ R. Filler and E. J. Piasek, *J. Org. Chem.* **29**, 2205 (1964).

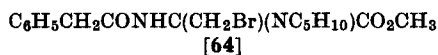
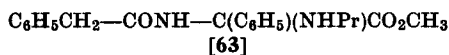
hydroxide only, a small amount of **61** accompanies the two products of $>\text{C}=\text{N}-$ cleavage.⁸⁶ Structures **60** and **61** are probably in rapid equilibrium, and the isolation of products derived from **60** does not provide evidence to support a preference of the 5(2*H*)-oxazolone over the 5(4*H*) form. Compound **62**, which can exist only in the 5(2*H*) form, gives phenylacetamide and $\text{C}_6\text{H}_5\text{COCO}_2\text{H}$ on mild alkaline hydrolysis.⁸⁷



(b) *Conjugate addition* of strong nucleophiles to the $>\text{C}=\text{N}-\text{C}=\text{C}<$ moiety, followed by ring opening of the resulting saturated 5(4*H*)-oxazolone. Thus, **57** reacts with simple or peptidic amino acid esters⁸⁸ [Eq. (31)]. Similarly, **62** gives **63** in methanolic *n*-propylamine,⁸⁷ and



the 4-bromomethyl analog of **57** (**62a**) yields **64** on treatment with methanolic piperidine.⁸⁴



Similar behavior of **62** with arylamines and hydrazines has recently been reported.^{87a}

Weak nucleophiles attack the 2-position with ring opening to form pyrrole derivatives after cyclization.⁸⁴ The bromopseudooxazolone **62a** yields the pyrroline **65** in methanolic potassium carbonate.

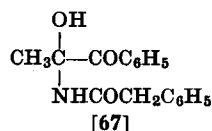
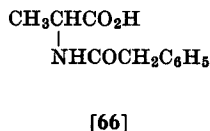
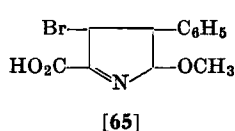
Catalytic hydrogenation of **57** affords 2-phenylacetamidopropionic acid (**66**) or its ester by solvolytic opening of the initially formed 5(4*H*)-oxazolone.⁸⁶ Lithium aluminum hydride reduction gives the

⁸⁷ G. Adembri, *Ann. Chim. (Rome)* **50**, 374 (1960).

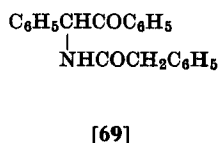
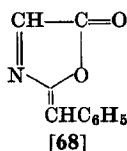
^{87a} A. Mustafa, M. K. Hilmy, A. E. Sammour, and M. M. N. Eldeen, *Tetrahedron* **20**, 1063 (1964).

⁸⁸ A. Romeo and A. M. Schimberni, *Atti Accad. Naz. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* **22**, 620 (1957); *Chem. Abstr.* **52**, 2837 (1958).

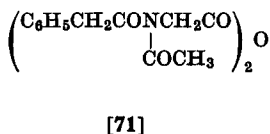
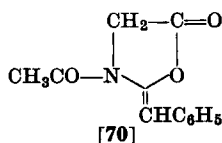
corresponding primary alcohol.⁸⁶ Compound **57** reacts with phenylmagnesium bromide to form a product whose properties suggest structure **67** in which the $>\text{C}=\text{N}-$ bond is hydrated.⁸⁶ The structure,



however, remains in doubt. 2-Benzylidene-5(2*H*)-oxazolone (**68**) reacts with two equivalents of benzene in the presence of anhydrous aluminum chloride to form **69** by addition and acylation.⁸⁶



Phenylacetic acid cyclizes in acetic anhydride to give 2-benzylidene-3-acetyl-5-oxazolidinone (**70**)⁸⁹; the previously proposed⁹⁰ anhydride structure **71** was shown to be incorrect. Compound **70** reacts



with benzaldehyde in acetic anhydride-potassium carbonate to form the azlactone **45** and *trans*- α -phenylcinnamic acid.^{78, 89} The reaction probably involves condensation of **70** with benzaldehyde, cleavage of the hetero ring, detachment of phenylacetic acid, recyclization to **45**, and condensation of the acid with benzaldehyde.

B. 2-TRIFLUOROMETHYLPSEUDOOXAZOLONES

Weygand *et al.*⁹¹⁻⁹³ prepared 4-alkyl-2-trifluoromethyl-5(4*H*)-oxazolones (**72**) by treating α -amino acids with trifluoroacetic

⁸⁹ S. I. Lur'e, E. S. Chaman, and M. M. Shemyakin, *J. Gen. Chem. USSR (Eng. Transl.)* **25**, 1751 (1955).

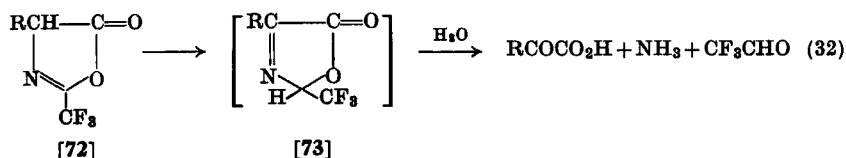
⁹⁰ I. T. Strukov, *J. Gen. Chem. USSR (Eng. Transl.)* **23**, 438 (1953).

⁹¹ F. Weygand and U. Glockler, *Chem. Ber.* **89**, 653 (1956).

⁹² F. Weygand and W. Steglich, *Angew. Chem.* **73**, 433 (1961).

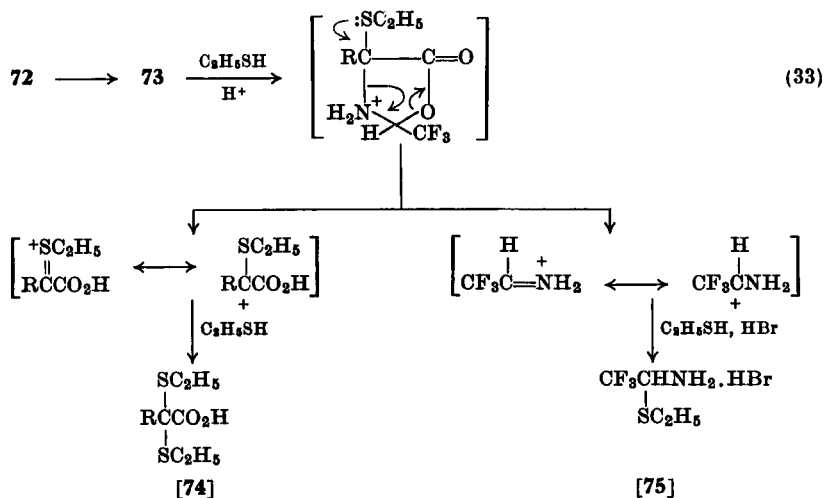
⁹³ F. Weygand, W. Steglich, and H. Tanner, *Ann. Chem.* **658**, 128 (1962).

anhydride or by cyclization of *N*-trifluoroacetyl (TFA) α -amino acids. These azlactones readily undergo a prototropic shift in acidic or alkaline media to form the isomeric 5(2*H*)-oxazolones (**73**), which hydrolyze to 2-oxo acids [Eq. (32)] in good yields.^{92, 93} The first non-enzymatic synthesis of an optically active 2-oxo acid was accomplished



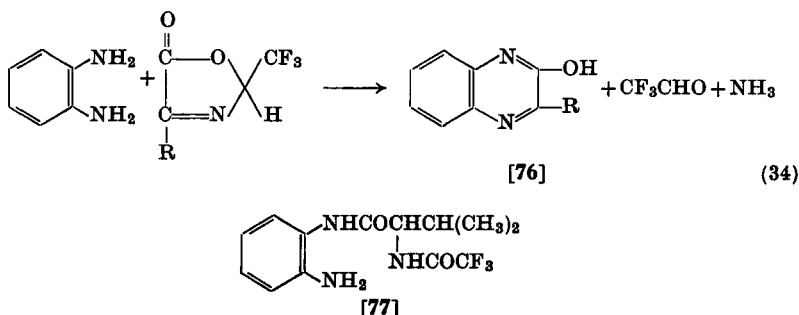
by this route. Thus, (+) 3-methyl-2-oxovaleric acid is prepared by hydrolysis of (+) 4-(2'-butyl)-2-trifluoromethyl-5(4*H*)-oxazolone in citric acid-phosphate buffer at pH 6.8.⁹³

Further evidence for a pseudooxazolone intermediate is the fragmentation of **72** by ethyl mercaptan in hydrobromic acid-acetic acid [Eq. (33)]. The mercaptal **74** hydrolyzes readily in acetic acid to give the 2-oxo acid.



The oxazolones react in the pseudo form with *o*-phenylenediamine [Eq. (34)] to give substituted quinoxalines (**76**)⁹³ in good yield. When R is an isopropyl group, a monoacylated product (**77**) is also isolated.

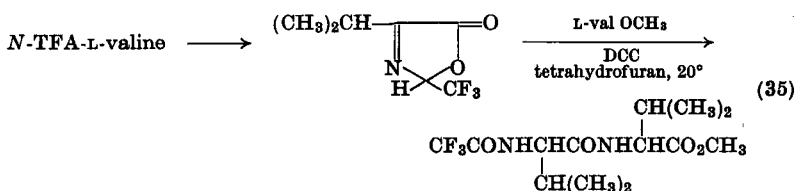
With monoamines, the oxazolones give the "normal" ring-opened products, *N*-TFA amino acid amides, but with aniline both forms



participate and the oxo acid anilide and *N*-TFA amino acid anilide are obtained. A third product, the *N*-TFA amino acid amide, arises from reaction of the azlactone with the liberated ammonia.

The rate of formation of the pseudooxazolone may be followed conveniently by proton magnetic resonance spectroscopy.⁹⁴

A reversal of the $5(4H) \rightleftharpoons 5(2H)$ equilibrium was established by demonstrating the presence of 4-isopropyl-2-trifluoromethyl-5(2*H*)-oxazolone as an intermediate in the reaction of *N*-TFA-L-valine with the methyl ester of L-valine [Eq. (35)]⁹⁵ using gas chromatography. The resulting product is a mixture of 74% L,L- and 26% D,L-*N*-TFA dipeptide methyl ester (see Section II, B, 4).



IV. 4-Oxazolin-2-ones

A. PREPARATION

The preparation of 3,5-diphenyl-4-oxazolin-2-one by reaction of phenacylaniline with phosgene was described by McCombie and Scarborough,⁹⁶ who also showed that the 3,4,5-triphenyl analog was an extremely stable compound which failed to react with a variety of

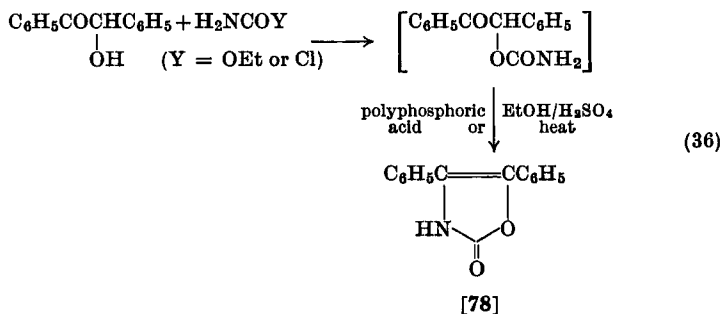
⁹⁴ F. Weygand, W. Steglich, D. Mayer, and W. von Philipsborn, *Chem. Ber.* **97**, 2023 (1964).

⁹⁵ F. Weygand, A. Prox, L. Schmidhammer, and W. König, *Angew. Chem. Intern. Ed. Engl.* **2**, 183 (1963).

⁹⁶ H. McCombie and H. A. Scarborough, *J. Chem. Soc.* **103**, 56 (1913).

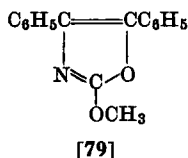
reagents, including boiling dilute acid and alkali, PCl_5 , bromine, aniline, and phenylhydrazine.

A more detailed study of the chemistry of these compounds has been carried out by Gompper *et al.*⁹⁷⁻¹⁰¹ and by de Stevens.¹⁰² It was observed⁹⁷ that α -hydroxy-ketones, such as benzoin, react with ethyl carbamate or carbamyl chloride to form a substituted carbamate, which, without isolation, cyclizes to a 2(3*H*)-oxazolone **78** [Eq. (36)].



In similar fashion, *N*-substituted-2(3*H*)-oxazolones were prepared directly from the hydroxy-ketone by reaction with urethanes in the presence of pyridine and dimethylformamide or by using isocyanates.

As expected, compounds of type **78** possess an acidic hydrogen and readily form *N*-acetyl derivatives. The acetyl group is removed by warming with aqueous ammonia, and it is replaced by a methyl group when the compound is treated with alkaline dimethyl sulfate or excess diazomethane.



N-Methylation occurs when **78** is treated with dimethyl sulfate or diazomethane, but reaction with silver oxide-methyl iodide gives a

⁹⁷ R. Gompper, *Chem. Ber.* **89**, 1748 (1956).

⁹⁸ R. Gompper, *Chem. Ber.* **89**, 1762 (1956).

⁹⁹ R. Gompper and H. Herlinger, *Chem. Ber.* **89**, 2816 (1956).

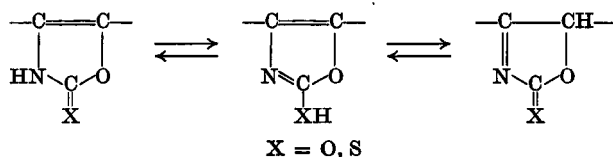
¹⁰⁰ R. Gompper and H. Herlinger, *Chem. Ber.* **89**, 2825 (1956).

¹⁰¹ R. Gompper, *Chem. Ber.* **90**, 374 (1957).

¹⁰² G. de Stevens, *J. Org. Chem.* **23**, 1572 (1958).

mixture of *N*- and *O*-methylated products, with the latter predominating. The latter reagent permits a convenient synthesis of 2-methoxy-4,5-diphenyloxazole (79).

The reaction of 78 with phosphorus pentasulfide⁹⁸ in xylene gives the corresponding 2-oxazolethione, which also forms the *N*-methyl product with dimethyl sulfate and 4,5-diphenyl-2-methylmercapto-oxazole in 98% yield on treatment with silver oxide-methyl iodide.

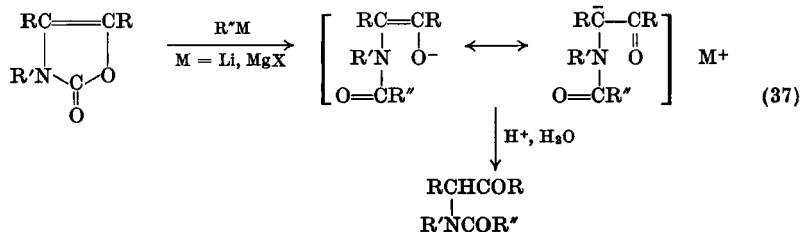


Although these reactions suggest the possibility of a tautomeric equilibrium between the amide and imidol forms in the *N*-unsubstituted compounds, the ultraviolet,⁹⁹ fluorescence,⁹⁹ and infrared spectra¹⁰⁰ of a series of such compounds support the amide structure only.

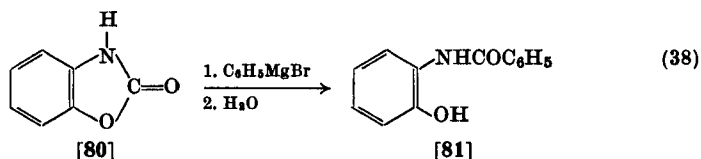
B. REACTIONS

Although the 2-oxazolones are inert to many reagents, they react readily with organometallic reagents¹⁰¹ to give α -acylamino ketones in 44–69% yield. For example, 3,4,5-triphenyl-4-oxazolin-2-one gives benzoyldesylaniline with phenylmagnesium bromide, and valeryldesylamine is obtained from reaction of the 4,5-diphenyl analog with *n*-butyllithium. The reaction may be visualized as proceeding by nucleophilic attack at the carbonyl carbon, followed by protonation of the resulting resonance-stabilized anion [Eq. (37)].

Similarly, benzoxazol-2-one (80) forms *o*-benzamidophenol (81) on

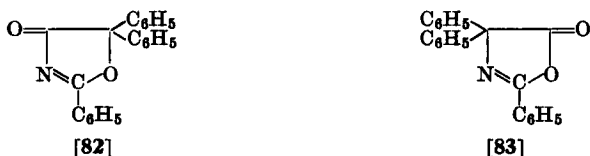


reaction with phenylmagnesium bromide or phenyllithium¹⁰³ [Eq. (38)]. The *N*-benzoyl analog also gives **81** and triphenylcarbinol.

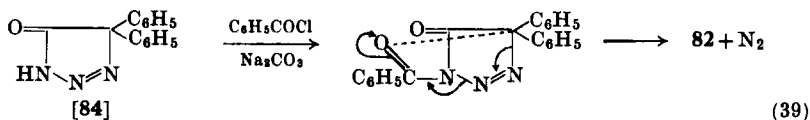


V. 2-Oxazolin-4-ones

The isolation in poor yield of 2,5,5-triphenyl-4(5*H*)-oxazolone (**82**) by reaction of benzoic acid with benzonitrile in concentrated sulfuric acid was claimed by Japp and Findlay.¹⁰⁴ Cornforth,¹⁰⁵ however, suggested that the reactions of this product, m.p. 136°, could be accounted for more satisfactorily by the isomeric 5(4*H*) structure **83**.



The preparation of **82**, m.p. 169°, was accomplished¹⁰⁶ by *N*-benzoylation and ring cleavage of 4,4-diphenyl-5-oxo-Δ²-1,2,3-triazoline (**84**) followed by ring closure [Eq. (39)]. This appears to be the only known example of an oxazolone of this type.



The structure of **82** was established by alkaline ring cleavage to benzoic acid amide and by hydrogenolysis to $(\text{C}_6\text{H}_5)_2\text{CH}-\text{CONH}-\text{COC}_6\text{H}_5$. These reactions also served to eliminate **83** as the structure of the 169° compound. The other possible isomeric structure, $(\text{C}_6\text{H}_5)_2\text{C}(\text{CN})\text{OCOC}_6\text{H}_5$, which could have formed after *O*-acylation, was ruled out by its independent synthesis from bromodiphenylacetonitrile and silver benzoate.

¹⁰³ A. Mustafa, W. Asker, and O. H. Hishmat, *J. Am. Chem. Soc.* **77**, 5127 (1956).

¹⁰⁴ F. R. Japp and A. Findlay, *J. Chem. Soc.* **75**, 1028 (1899).

¹⁰⁵ Ref. 1, p. 373.

¹⁰⁶ K. Hohenlohe-Oehringen, *Monatsh. Chem.* **89**, 588 (1958).

Isothiazoles

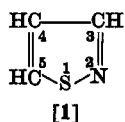
R. SLACK and K. R. H. WOOLDRIDGE

*The Research Laboratories, May & Baker Ltd.,
Dagenham, Essex, England*

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I. Introduction

"Isothiazole is the sulfur analogue of isoxazole. No member of the group is known. A necessary condition for the development of this field is the preparation of the unknown thiohydroxylamine." This reasonable assessment¹ of the position in 1947 was not in fact true.



The chemistry of mononuclear isothiazoles has been developed since 1956 without the aid of thiohydroxylamine, the preparation of this very unstable substance having only recently been reported.² Bicyclic and polycyclic systems involving the isothiazole (1,2-thiazole) structure have long been known and were fully reviewed in 1952,³ but little new work has been reported since then and the present review

¹ V. von Richter, "The Chemistry of the Carbon Compounds," 3rd English Edn., Vol. 4, p. 123. Elsevier, New York, 1947.

² R. Gösl and A. Meuwesen, *Z. Anorg. Allgem. Chem.* **314**, 334 (1962).

³ L. L. Bambas, "The Chemistry of Heterocyclic Compounds," Vol. IV, p. 225. Interscience, New York, 1952.

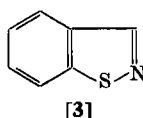
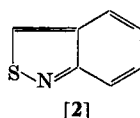
will be restricted to mononuclear compounds. The parent compound (1) was first described by Adams and Slack⁴ in 1956 and some 250 derivatives have now been reported.

II. Preparation of Isothiazoles

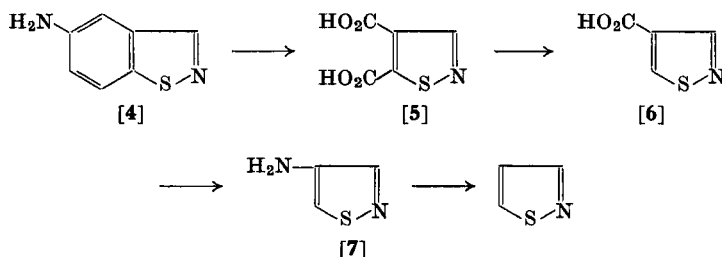
A. GENERAL METHODS

1. From Benzisothiazoles

There are two series of benzisothiazoles, derived from benz[*c*]isothiazole (2) and benz[*d*]isothiazole (3), and both, if the benzene ring were suitable weakened, could doubtless be oxidized to isothiazole-dicarboxylic acids. In their first synthesis^{4,5} Adams and Slack



oxidized 5-aminobenz[*d*]isothiazole (4) with potassium permanganate to give the dicarboxylic acid 5, which decarboxylated smoothly on heating to give isothiazole-4-carboxylic acid (6). Degradation to 4-aminoisothiazole (7) followed by reductive deamination gave



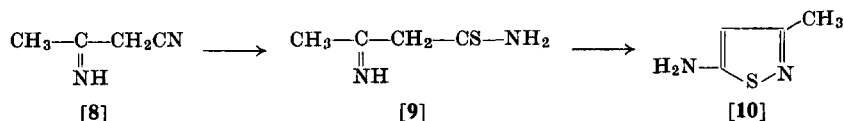
isothiazole. This tedious preparation, involving eight stages from the aminobenzisothiazole, was clearly unsuitable as a general method and an alternative route, involving the formation of the N-S bond by oxidation, was devised.

2. From Iminothioamides

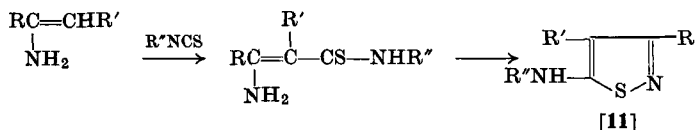
Adams and Slack's second isothiazole synthesis⁵ involved the preparation of β -iminothiobutyramide (9) from the nitrile 8 and cycliza-

⁴ A. Adams and R. Slack, *Chem. & Ind. (London)* 1232 (1956).

⁵ A. Adams and R. Slack, *J. Chem. Soc.* 3061 (1959).



tion with chloramine or, better, hydrogen peroxide or salts of peracids to give 5-amino-3-methylisothiazole (10). This synthesis has been extended by Goerdeler and his co-workers^{6-8, 8a} to give a variety of

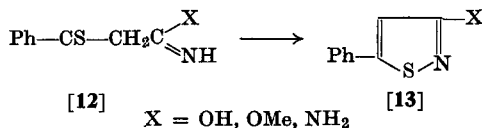


R = Me, Ph

R' = H, CN, CO₂Et, CONH₂, COCH₃

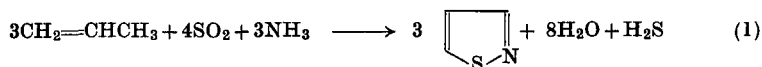
R'' = H, Me, Ph, CO₂Ph, COPh, etc.

substituted 5-aminoisothiazoles (11). In a further variation, Goerdeler and Mittler used the appropriate thioketone (12) to obtain the first examples of 3-hydroxy-, -methoxy-, and -amino-isothiazoles (13).⁹



3. From Olefins

Hübenett and his colleagues have shown that propylene reacts with sulfur dioxide and ammonia in the presence of a catalyst such as activated alumina to give a high yield of isothiazole [Eq. (1)].¹⁰ This reaction is applicable to certain substituted propenes; thus, isobutylene



⁶ J. Goerdeler and H. W. Pohland, *Angew. Chem.* **72**, 77 (1960); J. Goerdeler and H. W. Pohland, *Chem. Ber.* **94**, 2950 (1961).

⁷ J. Goerdeler and H. W. Pohland, *Chem. Ber.* **96**, 526 (1963).

⁸ J. Goerdeler and H. Horn, *Chem. Ber.* **96**, 1551 (1963).

^{8a} J. Goerdeler, *Angew. Chem. Intern. Ed. Engl.* **2**, 693 (1963).

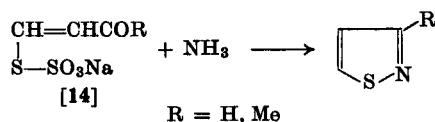
⁹ J. Goerdeler, *Angew. Chem.* **74**, 498 (1962); J. Goerdeler and W. Mittler, *Chem. Ber.* **96**, 944 (1963).

¹⁰ F. Hübenett, F. H. Flock, and H. Hofmann, *Angew. Chem. Intern. Ed. Engl.* **1**, 508 (1962).

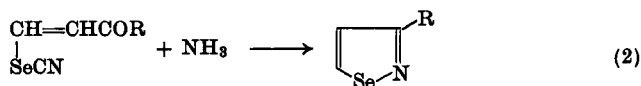
gives 4-methylisothiazole, and α -methylstyrene gives 4-phenylisothiazole. Olefin isomerization may, however, occur, and 1- or 2-butene gives a mixture of 3- and 5-methylisothiazole. Yields, particularly with the simpler compounds, are good for a catalytic process (25–65%), and the reaction temperatures (200°) emphasize the inherent stability of isothiazoles.^{11, 21}

4. From Acetylenes

An elegant synthesis of both isothiazole and 3-methylisothiazole has been reported by Wille and his co-workers.¹² This depends on the cyclization with liquid ammonia of the *cis* form of the addition product **14** which is obtained from the appropriate acetylenic carbonyl



compounds and sodium thiosulfate. It was incorrectly reported in a preliminary communication¹² that an analogous cyclization of acrolein-3-thiocyanate gives a 55% yield of isothiazole. The yield is, in fact, only 4%, the *cis*-thiocyanate adduct being extremely unstable. The main product is an isomeric linear amine.¹³ This method is also applicable to the synthesis of isoselenazole and its simple derivatives [Eq. (2)].¹⁴



2-Alkylisothiazol-3-ones have been prepared by a similar reaction.^{14a}

5. From Dithiolium Salts

Certain dithiolium salts have been reported by Leaver and Robertson¹⁵ to form isothiazoles on treatment with ammonia; thus, 3,5-diphenyl-1,2-ditholium perchlorate (**15**) gives a 50% yield of 3,5-diphenylisothiazole (**16**). The method does not appear to be generally applicable, and the analogous 3-methyl-5-phenyl-1,2-dithiolium salt did not give an isothiazole.

¹¹ F. Hübennett and H. Hofmann, *Angew. Chem. Intern. Ed. Engl.* **2**, 325 (1963).

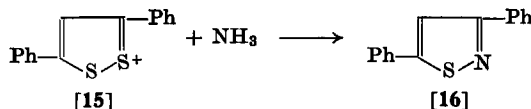
¹² F. Wille, L. Capeller, and A. Steiner, *Angew. Chem. Intern. Ed. Engl.* **1**, 335 (1962).

¹³ F. Wille, personal communication.

¹⁴ F. Wille, A. Ascherl, G. Kaupp, and L. Capeller, *Angew. Chem.* **74**, 753 (1962).

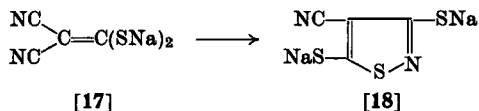
^{14a} W. D. Crow and N. J. Leonard, *Tetrahedron Letters* 1477 (1964).

¹⁵ D. Leaver and W. A. H. Robertson, *Proc. Chem. Soc.* 252 (1960).



6. From Dicyanoethylene Dithiolate

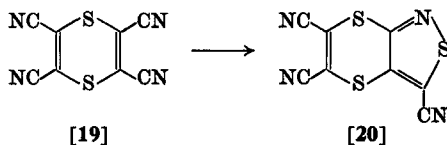
Soederbaeck¹⁶ cyclized the readily available dicyanoethylene-dithiolate (17) with sulfur to give a trisubstituted isothiazole (18).



The same reaction was reported independently by Hatchard,^{17, 17a} who also obtained 4-cyano-3,5-dichloroisothiazole^{17b} and the disodium salt of 4-cyano-3-hydroxy-5-mercaptoisothiazole by carrying out the ring closure with chlorine and hydrogen peroxide, respectively.

7. From Cyanocarbon Sulfides

Although not presented specifically as a potential synthesis of mononuclear derivatives, the ready conversion of cyanocarbon sulfides (19) into condensed ring isothiazoles (20) is of interest and may provide new approaches to simpler isothiazoles.¹⁸



B. 4-SUBSTITUTED ISOTHIAZOLES

The 4-position of isothiazole is attacked by electrophilic reagents, and many simple derivatives are thus readily available by direct substitution followed, if necessary, by suitable transformation of the group introduced. For example, bromination of 3-methylisothiazole

¹⁶ E. Soederbaeck, *Acta Chem. Scand.* **17**, 362 (1963).

¹⁷ W. R. Hatchard, *J. Org. Chem.* **28**, 2163 (1963).

^{17a} W. R. Hatchard, *J. Org. Chem.* **29**, 665 (1964).

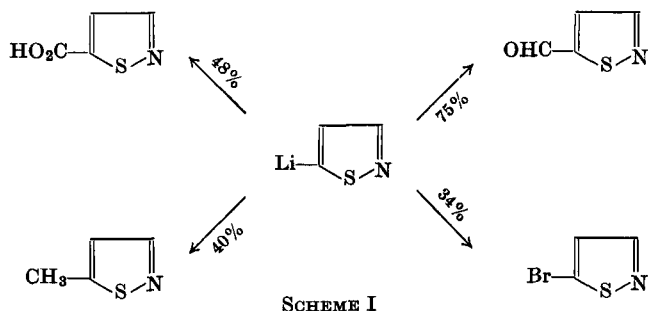
^{17b} W. R. Hatchard, *J. Org. Chem.* **29**, 660 (1964).

¹⁸ H. E. Simmons, R. D. Vest, D. C. Blomstrom, J. R. Roland, and T. L. Cairns, *J. Am. Chem. Soc.* **84**, 4746 (1962); A. Schoor, E. Jacobi, S. Lust, H. Flemming, and O. W. Müller, U.S. Pat. 3,000,780 (1959); H. E. Simmons, British Pat. 891,093 (1959); W. R. Hatchard, U.S. Pat. 3,048,596 (1962).

gives 4-bromo-3-methylisothiazole from which the corresponding nitrile and carboxylic acid may easily be obtained.¹⁹ Again, 4-aminoisothiazole has been obtained by nitration of isothiazole and reduction of the nitro compound with stannous chloride.²⁰ Isothiazole-4-sulfonic acid and -sulfonyl chloride have been reported,²¹ but formylation, with dimethylformamide and phosphorus oxychloride, and acylation, under Friedel-Crafts conditions, have not been successful.¹⁹

C. 5-SUBSTITUTED DERIVATIVES

5-Halogenoisothiazoles and isothiazoles unsubstituted in the 5-position lithiate readily at -70° with *n*-butyllithium.^{19, 29} These lithium derivatives react normally to give a variety of substituted isothiazoles as indicated in Scheme I (yields shown on arrows). This



method is of wide utility and is applicable to isothiazoles with halogeno, alkyl, or carboxy substituents. A few failures have been reported; for example, 3-methyl-4-nitroisothiazole does not react.

III. Properties of Isothiazoles

A. PHYSICAL PROPERTIES

1. Physical Characteristics of Isothiazoles

Isothiazole, like its simple alkyl derivatives, is a mobile, colorless liquid, d_4^{20} 1.1706,¹⁰ n_D^{20} 1.5320,⁵ b.p. 114° ,¹⁰ with an odor resembling

¹⁹ D. Buttimore, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.* 2032 (1963).

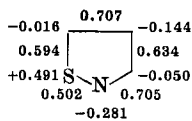
²⁰ M. P. L. Caton, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.* 446 (1964).

²¹ F. Hübenett, F. H. Flock, W. Hansel, H. Heinze, and H. Hofmann, *Angew. Chem. Intern. Ed. Engl.* 2, 714 (1963).

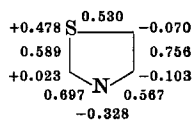
that of pyridine. It is approximately 3.5% soluble in water. Isothiazole is a good solvent for many organic substances but should be used with caution since its toxicity (as judged by its acute effect on laboratory animals) is considerably greater than that of pyridine. The more highly substituted derivatives are usually far less toxic.

2. Electron Density Diagram

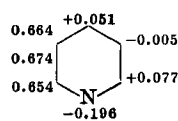
Adams and Slack⁵ compared the electron densities and mobile bond orders of the parent molecule (21) with those of thiazole (22) and pyridine (23). Overlap was neglected in these simplified calculations,



[21]



[22]



[23]

but the magnitude of the bond orders emphasized the inherent stability of the isothiazole structure. This has since been confirmed by a consideration of its chemical behavior and by nuclear magnetic resonance spectroscopy²³ (cf. Section III, A, 3, c).

3. Spectroscopic Studies

a. *Ultraviolet Absorption Spectra.* Isothiazole shows an absorption maximum at $244 \text{ m}\mu$ ($\epsilon = 5210$) analogous to that of similar heterocyclic systems such as thiazole. The presence of substituents causes a bathochromic shift of this band, the effect varying with the nature of the substituent and its position in the isothiazole ring. These displacements, which are additive and remarkably consistent, have been calculated for a variety of substituents. Predicted and observed figures for this band agree to within $\pm 3 \text{ m}\mu$ for a wide range of mono-, di-, and tri-substituted isothiazoles.^{19, 20, 29}

b. *Infrared Spectra.* Analogously with other 5-membered heterocyclic ring systems, three bands of medium intensity are normally encountered in the $1600\text{--}1300 \text{ cm}^{-1}$ region of the spectrum. The bands characteristic of the isothiazole nucleus occur at or near 1510 , 1400 , and 1340 cm^{-1} , although one or more, particularly the 1340 cm^{-1} band, may be weak or unobservable.^{6, 22} The 1400 cm^{-1} peak is relatively

²² T. L. Threlfall, personal communication.

²³ J. A. Elvidge, personal communication.

insensitive to substituent effects, but the 1510 cm^{-1} peak may be displaced to $1555\text{--}1565\text{ cm}^{-1}$ in the case of amino and hydroxy derivatives.⁹ Weak, broad bands near 1620 and 1030 cm^{-1} are overtones of ring vibrations at 810 and 500 cm^{-1} . Ring vibrations give rise to one or more fundamental bands between 1300 and 900 cm^{-1} in all isothiazoles, but these are sensitive to substitution effects, and correlations can only be made in closely related series. The strongest band in the spectra of simple isothiazoles is often found near 810 cm^{-1} except for isothiazole quaternary salts and 4-carboxylic acids, which show a band in the region $870\text{--}830\text{ cm}^{-1}$, and 4-monosubstituted compounds, for which it is displaced to about 780 cm^{-1} (the band at 810 cm^{-1} in the latter class of compounds is probably the hydrogen out-of-plane deformation). This band is relatively insensitive to substituent effects.

In isothiazoles carrying unsubstituted ring hydrogen atoms, the hydrogen stretching vibration gives rise to a band near 3100 cm^{-1} . The very strong hydrogen out-of-plane deformation, which occurs in the spectrum of isothiazole at 733 cm^{-1} , appears in monosubstituted compounds as a medium band at $830\text{--}730\text{ cm}^{-1}$. For disubstituted compounds it appears at $900\text{--}820\text{ cm}^{-1}$, but this band is too weak to observe in many cases. The vibrations due to substituents on the isothiazole ring appear to be essentially as expected in most cases. The carbonyl stretching frequency of esters lies near 1720 cm^{-1} and of aldehydes near 1690 cm^{-1} . Carboxylic acids show a carbonyl stretching band at higher frequencies, usually between 1710 and 1720 cm^{-1} , but with some 5-carboxylic acids it may be as high as 1750 cm^{-1} .²² See also reference 23a.

c. *Nuclear Magnetic Resonance Spectra*. Proton chemical shift data have been used to estimate the aromatic character of isothiazole as defined by the ability to sustain an induced ring current. The results indicate that isothiazole has approximately the same aromaticity as benzene,²³ a result which is in accordance with many of the chemical properties of isothiazole.

B. PREPARATION AND CHEMICAL PROPERTIES

1. Isothiazole

On the laboratory scale, isothiazole is most conveniently prepared by the acetylenic route.¹² On the other hand, the olefinic route¹⁰ has

^{23a} S. Califano, F. Piacenti, and G. Sbrana, *Spectrochim. Acta* **20**, 339 (1964).

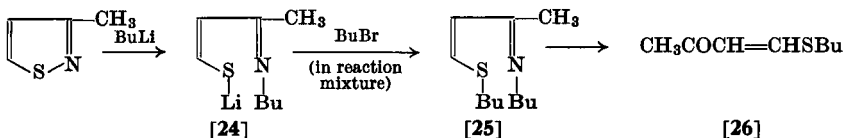
great potentialities as a source of cheap isothiazole on an industrial scale.

The substitution properties of isothiazole are in broad agreement with the electron distribution pattern.¹⁹ Thus, electrophilic substitution occurs predominantly in the 4-position, if this is free, and metalation in the 5-position. The ring appears to be stable to acid, alkali, and mild oxidation and forms a chloroplatinate and an unstable mercurichloride.⁵

2. Substituted Isothiazoles

a. *Alkyl Derivatives.* All the possible monomethyl- and dimethyl-isothiazoles are known and, with the exception of 3,5-dimethyl-isothiazole, have been prepared by the olefin route.^{10,21} 3-Methyl-isothiazole is conveniently prepared by deamination of 5-amino-3-methylisothiazole¹⁹ or from acetylacetylene.¹² It has also been made by thermal decarboxylation of 3-methylisothiazole-5-carboxylic acid. 5-Methyl- and 3,5-dimethyl-isothiazole have been prepared from the appropriate isothiazol-5-yl lithium compounds and methyl iodide.²⁰

3- and 5-Methylisothiazoles undergo normal electrophilic attack in the 4-position,^{5,19-21,23b} but sulfonation of 4-methylisothiazole does take place in low yield to give (probably) 4-methylisothiazole-5-sulfonic acid.²¹ Halogenation occurs mainly in the 4-position,^{23b} but small amounts of other halogenated isothiazoles have been observed as by-products.²¹ Side-chain halogenation has also been reported.^{21,29} 3- and 4-Methylisothiazoles lithiate in the 5-position in high yield, but it appears that under certain conditions ring scission may occur at the N-S bond, for example 4-butylmercapto-2-oxo-but-3-ene (**26**) is formed²⁰ as a by-product during the lithiation of 3-methylisothiazole and subsequent formylation with dimethylformamide. It seems likely that **26** is derived from the intermediates **24** and **25**. This is the first clearly documented case of isothiazole ring scission.



Benzaldehyde does not condense with any of the three monomethyl isothiazoles, but 3-nitrobenzaldehyde gives 1-(isothiazol-5'-yl)-2-(3'-nitrophenyl)-ethylene with the 5-methyl derivative. Reactivity

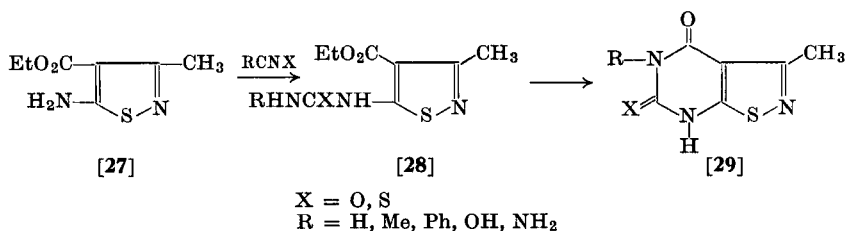
^{23b} F. Piacenti, P. Bucci, and P. Pino, *Chim. Ind. (Milan)* **46**, 207 (1964).

is enhanced by the introduction of a nitro group into the 4-position of the isothiazole.²¹

b. *Arylisothiazoles*. A mixture of 3-, 4-, and 5-phenylisothiazoles has been obtained by decomposing benzoyl peroxide at 100° in the presence of isothiazole.¹¹ By the olefin route, 4-phenylisothiazole has been obtained from α -methylstyrene and 5-phenylisothiazole from β -methylstyrene or allylbenzene. Phenylisothiazoles are colorless, distillable liquids and have odors reminiscent of benzonitrile.¹¹ 3,5-Diphenylisothiazole has been prepared from 3,5-diphenyl-1,2-dithiolium perchlorate and ammonia.¹⁵

c. *Nitro Derivatives*. Only examples of the 4-nitro series have been reported. These derivatives have been prepared in high yield by nitration with concentrated sulfuric and fuming nitric acids or with sulfuric acid and potassium nitrate. 3- or 5-Alkyl,^{5, 21} 5-halogeno,⁵ and 5-acylamido groups^{5, 23c} do not interfere, but 5-amino groups undergo *N*-nitration to give 5-nitramino derivatives.⁵ 4-Nitroisothiazoles are valuable intermediates in the preparation of 4-amino compounds, to which they have been reduced, usually in good yield, by stannous chloride,²⁰ or ferrous sulfate and ammonia,⁵ or in the presence of catalysts (one example of a highly substituted compound).⁵

d. *Amino Derivatives*. Most 5-aminoisothiazoles described in the literature have been prepared by the iminothioamide route (see Section II, A, 2). 5-Aminoisothiazoles diazotize normally in strong acids and the diazonium salts couple with β -naphthol,⁶⁻⁸ deaminate on reaction with hypophosphorous acid,¹⁹ and undergo the Sandmeyer reaction to give halogeno compounds^{5, 6, 19} but not nitriles.⁵ The 5-amino group acylates normally^{5, 9, 24} and forms ureas and thioureas



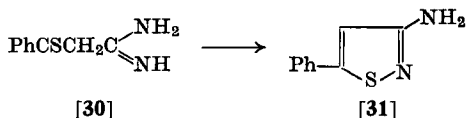
with isocyanates and isothiocyanates. The ureas and thioureas (28) derived from 5-amino-4-ethoxycarbonyl-3-methylisothiazole (27) have been used to synthesize isothiazole analogues of xanthine and thioxanthine (29).⁸

^{23c} M. Robba and R. C. Moreau, *Ann. Pharm. Franc.* **22**, 14 (1964).

5-Amino-3-methylisothiazole halogenates readily in the 4-position,¹⁹ but nitration leads to the formation of a nitramino compound.⁵ Acylaminoisothiazoles nitrate normally.⁵

4-Aminoisothiazoles have all been prepared by nitration and subsequent reduction, usually in good yield,⁵ although the reduction of 4-nitroisothiazole to 4-aminoisothiazole has only been achieved in 35% yield.²⁰ 4-Aminoisothiazoles behave as normal aromatic amines⁵ and the diazonium salts undergo the Sandmeyer reaction²⁰ and reductive deamination.⁵

The only example of a 3-aminoisothiazole so far described is 3-amino-5-phenylisothiazole (**31**), which is formed by oxidative cyclization of thiobenzoylacetylamine (**30**).⁹ Compound **31** brominates normally, but diazotization and coupling with β -naphthol give a mixture of the azo compound and 3-hydroxy-5-phenylisothiazole.⁹



3-Amino-5-phenylisothiazole is slightly less basic (pK 2.27) than the isomeric 5-amino-3-phenylisothiazole (pK 2.65).⁶ Both 3- and 5-aminoisothiazoles can theoretically exist in tautomeric forms, but the presence of bands in the infrared spectrum at 3490 and 3400 cm^{-1} (in CCl_4) indicates that, at least in the case of 3-amino-5-phenylisothiazole, the amino form predominates.⁹ See also reference 17b.

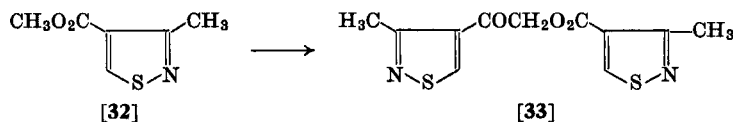
e. *Halogeno Derivatives.* 5-Halogenoisothiazoles, obtained from 5-aminoisothiazoles by the Sandmeyer reaction^{5, 6, 19} and by the action of bromine on lithium derivatives of isothiazole,²⁰ give nitriles with cuprous cyanide and 5-lithium derivatives at -70° with butyllithium.²⁰ Nitration takes place normally to give 4-nitro derivatives⁵ in which the halogen is activated by the adjacent nitro group; thus, 5-bromo-3-methyl-4-nitroisothiazole and sodium iodide at 100° afford 5-iodo-3-methyl-4-nitroisothiazole.⁵ See also reference 17b.

4-Halogeno compounds have been prepared by direct halogenation^{19, 21, 23b} or by Sandmeyer reaction on 4-aminoisothiazoles.²⁰ As expected from general considerations, a halogen atom in the 4-position is less reactive than one in the 5-position, but nitriles are obtained in good yield with cuprous cyanide at elevated temperatures.¹⁹ With butyllithium, lithiation occurs exclusively in the 5-position, and no evidence of halogen displacement has been obtained.²⁰

3-Chloro-4-methylisothiazole is formed by chlorination of 4-methylisothiazole under the influence of irradiation, together with an equal quantity of 4-chloromethylisothiazole.²¹ Side-chain halogenation of 3-methylisothiazoles has also been carried out with *N*-bromosuccinimide to give bromomethyl and dibromomethyl derivatives.²⁹ See also reference 17b.

f. *Carboxy Derivatives*. Isothiazole-5-carboxylic acids are most conveniently prepared by carbonation of the 5-lithio derivatives.²⁰ 3-Methylisothiazole-5-carboxylic acid has also been prepared by alkaline hydrolysis of the 5-nitrile.¹⁹ The 5-acids decarboxylate readily at or near their melting points^{5, 19} but otherwise behave normally, forming acid chlorides,^{9, 20} esters,^{5, 19, 20} amides,¹⁹ hydrazides,^{5, 19} and nitriles.¹⁹ The esters undergo the Claisen condensation to form β -ketoesters,¹⁹ and the nitriles form thioamides with hydrogen sulfide in pyridine.⁵ An anomalous reaction is the reduction of 5-cyano-3-methylisothiazole under Stephen's conditions to give 5-amino-methyl-3-methylisothiazole rather than the aldehyde.¹⁹

Simple isothiazole-4-carboxylic acids have been made from the corresponding nitriles,^{19, 20} which are available in turn from the halogeno derivatives, or directly by the olefin route.¹¹ 5-Aminoisothiazole-4-esters and -nitriles are readily obtained by the thioamide route. The 4-acids behave normally and form acid chlorides,^{5, 19, 20} esters,^{5, 19, 20} amides,²⁰ and hydrazides.^{19, 20} In contrast to the 5-series 4-carboxylic acids cannot easily be decarboxylated, and, in fact, isothiazole-4-carboxylic acid was first prepared by decarboxylation of isothiazole-4,5-dicarboxylic acid.⁵ The 4-acids will lithiate in the 5-position, but 4-methoxycarbonyl-3-methylisothiazole (**32**) appears to lithiate preferentially on the ester methyl group to give the keto ester **33**.²⁰



Isothiazole-3-carboxylic acid and its 4-bromo derivative have been obtained by oxidation of the corresponding aldehydes with silver oxide. They form acid chlorides, esters, and amides. The amides may be dehydrated to give the corresponding nitriles.²⁹

g. *Carbonyl Derivatives*. 5-Formylisothiazoles are readily available from isothiazolylolithium derivatives and dimethylformamide.²⁰

Aldehydes have also been obtained by lithium trialkoxyaluminum hydride reduction of 5-nitriles or 5-acid chlorides, and, as the thiosemicarbazones, by the McFadyen-Stevens reaction in surprisingly good yields (50–60%) considering the severity of the reaction conditions.¹⁹

5-Acetylisothiazoles have been prepared by ketonic hydrolysis of the β -ketoesters derived from the Claisen condensation on 5-ethoxycarbonylisothiazoles. 5-Acetyl-3-methylisothiazole is also obtained from the reaction of 5-cyano-3-methylisothiazole with methylmagnesium iodide.¹⁹

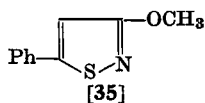
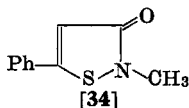
4-Formyl-3-methylisothiazole is prepared by hydrolysis of the appropriate Reissert compound and, as the thiosemicarbazone, in poor yield by the McFadyen-Stevens reaction.¹⁹ 4-Formylisothiazole has been obtained by oxidation of 4-methylisothiazole although no details of the preparation have been reported.²¹

3-Formyl- and 4-bromo-3-formyl-isothiazole have been prepared in good yield from the dibromomethyl compounds obtained by side-chain halogenation of the appropriate 3-methylisothiazole with *N*-bromosuccinimide. 3-Acetyl- and 3-acetyl-4-bromo-isothiazole have been prepared from the 3-cyanoisothiazoles and methyl magnesium iodide.²⁹

In general, the carbonyl derivatives of isothiazole behave normally and condense readily with carbonyl reagents. The aldehydes reduce ammoniacal silver nitrate and undergo the Cannizzaro reaction.¹⁹

h. Hydroxy Derivatives. No 4- or 5-hydroxyisothiazoles have been described. 3-Hydroxyisothiazoles have been prepared by oxidative cyclization of thioacylacetamides (cf. Section II, A, 2). They brominate normally and give colors with ferric chloride in water or ethanol. In 50% aqueous ethanol 3-hydroxy-5-phenylisothiazole has a *pK* of 7.48 and 3-hydroxy-5-methylisothiazole a *pK* of 8.15.

3-Hydroxyisothiazoles can theoretically exhibit keto-enol tautomerism and methyl derivatives of both the keto (34)^{9, 14a} and enol (35)⁹ forms have been synthesized by ring closure of the appropriate



intermediate. In methanolic solution, the UV spectra of 3-hydroxy-5-phenylisothiazole and 3-methoxy-5-phenylisothiazole are very similar suggesting that the enol form predominates. The fact that

3-hydroxy-5-phenylisothiazole and diazomethane give predominantly the *N*-methyl derivative (34) after 3 days⁹ is not inconsistent with this observation since the rate of interconversion of the tautomers is much faster than their reaction with diazomethane. See also reference 30.

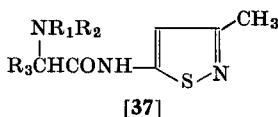
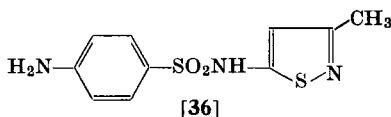
C. BIOLOGICAL PROPERTIES

Little has been published on the toxicity of simple isothiazoles except that isothiazole itself is much more toxic than pyridine.^{10, 21} More complex isothiazoles are undoubtedly less toxic.

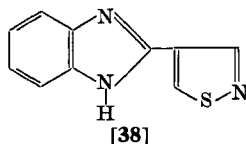
A novel simple heterocyclic system such as isothiazole has considerable potential in the fields of chemotherapy and pharmacology, and several examples are already known.

5-*p*-Aminobenzenesulfonamido-3-methylisothiazole (36),^{5, 24} known as sulfasomizole,²⁵ is a sulfonamide with a medium duration of action and has been on the market in Great Britain since 1962.

Uyeo and his colleagues have examined a series of 5-(aminoacylamido)-3-methylisothiazoles (37) for their analgesic action and claim that some are more potent than aminopyrine.²⁶



Several isothiazolyl derivatives (38) are included in a series of benzimidazoles claimed to have anthelmintic activity.²⁷



Thiosemicarbazones of 5-formyl- and 5-acetyl-isothiazoles are reported to have high activity against the pox group of viruses.²⁸

²⁴ A. Adams and R. Slack, British Pat. 835,753 (1960); A. Adams and R. Slack, British Pat. 835,754 (1960).

²⁵ A. Adams, W. A. Freeman, A. Holland, D. Hossack, J. Inglis, J. Parkinson, H. W. Reading, K. Rivett, R. Slack, R. Sutherland, and R. Wien, *Nature* **186**, 221 (1960).

²⁶ S. Uyeo, H. Fujimura, and A. Asai, *Yakugaku Zasshi* **83**, 195 (1963).

²⁷ L. H. Sarett and H. D. Brown, Belgian Pat. 599,143 (1961).

²⁸ R. Slack, S. Squires, and K. R. H. Wooldridge, Belgian Pat. 614,993 (1962).

²⁹ D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.* 3114 (1964).

³⁰ N. J. Leonard and G. E. Wilson, *Tetrahedron Letters* 1471 (1964).

Hetarynes

H. J. DEN HERTOOG and H. C. VAN DER PLAS

*Laboratory of Organic Chemistry of the Agricultural University,
Wageningen, The Netherlands*

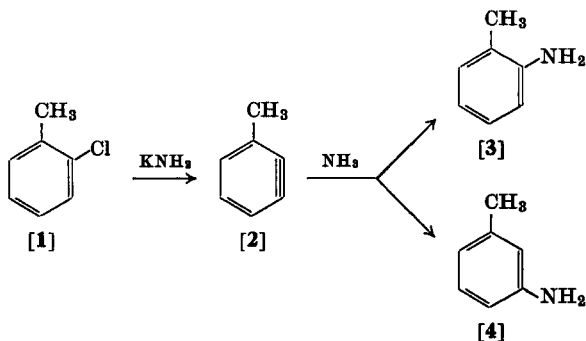
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I. Introduction

Prior to 1960 little work had been done on reactions of heterocyclic compounds involving hetarynes,¹ i.e. intermediates with a "triple bond" in the nucleus containing the hetero atom. Since then interest in hetarynes has grown and investigations in this area are developing rapidly using information available from carbocyclic aryne chemistry. Therefore, a short survey of the chemistry of arynes is presented before summarizing typical problems encountered in hetaryne chemistry.

Arynes are intermediates in certain reactions of aromatic compounds, especially in some nucleophilic substitution reactions. They are generated by abstraction of atoms or atomic groups from adjacent positions in the nucleus and react as strong electrophiles and as dienophiles in fast addition reactions. An example of a reaction occurring via an aryne is the amination of *o*-chlorotoluene (1) with potassium amide in liquid ammonia. According to the mechanism given, the intermediate 3-methylbenzyne (2) is first formed and subsequent addition of ammonia to the "triple bond" yields *o*-aminotoluene (3) and *m*-aminotoluene (4). It was found that partial re-arrangement of the *ortho* to the *meta* isomer actually occurs.

¹ This nomenclature was first used in a paper by T. Kauffmann and F. P. Boettcher [*Chem. Ber.* **95**, 949 (1962)].



Rearrangements during reactions of aromatic compounds with strong nucleophiles have been observed since the beginning of organic structural chemistry, and it was to explain these phenomena that the aryne hypothesis was first introduced. The first aryne structure was proposed by Stoermer and Kahlert² in 1902. After 1945, some important introductory work was done, especially by Wittig, but in a sense aryne chemistry is not older than ten years as in 1953–54 a solid base for its development was laid by Roberts and Huisgen and their groups.

It has been established that arynes are formed in the following classes of reaction:

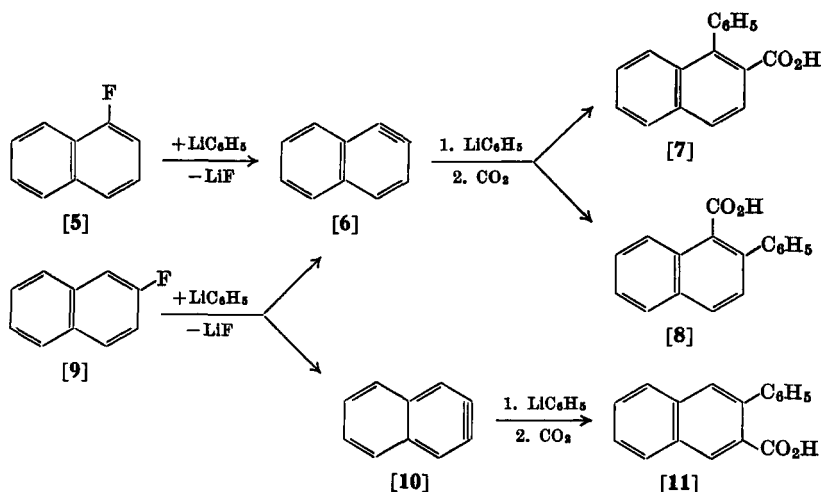
- (1) Action of alkali amides and alkyl- and aryl-lithiums on monohalogeno aromatic compounds,
- (2) Heating of aryl halides or aryl sulfonates with alkali hydroxide,
- (3) Treatment of dihalogeno aromatics with lithium amalgam, magnesium, zinc, etc.,
- (4) Heating of *ortho*-arenediazonium carboxylates or 1,2,3-arenothiadiazole-1,1-dioxides,
- (5) Heating of *ortho*-iodoarenemercuric iodides.

There is sound evidence for the existence of aryne intermediates as indicated by the following experiments, which also illustrate their reactivity.

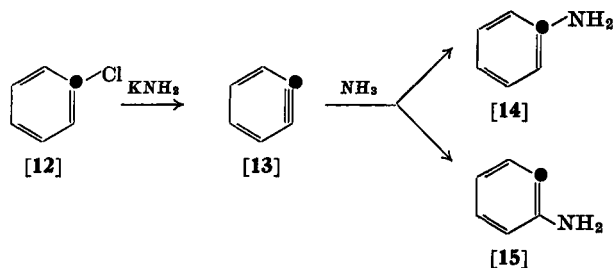
(1) Both 1- (5) and 2-fluoronaphthalene (9) yield with phenyllithium the same *asymmetrical* aryne (6): after subsequent carbonylation, mixtures containing 1-phenylnaphthalene-2-carboxylic acid (7) and 2-phenylnaphthalene-1-carboxylic acid (8) in the ratio 1:1.7 were

² R. Stoermer and B. Kahlert, *Ber.* **35**, 1633 (1902).

obtained in both cases. From 2-fluoronaphthalene (9) a third isomeric acid (11) is also formed, probably via the symmetrical aryne (10).³



(2) Evidence for *symmetrical* intermediates such as benzyne cannot be established by quantitative analysis of the reaction mixture unless a labelled starting substance is used. By applying labeling techniques, Roberts and his collaborators⁴ obtained results which indicated that benzyne (**[13]**) occurs as an intermediate in the amination of chlorobenzene with potassium amide in liquid ammonia. From chlorobenzene-1- C^{14} (**[12]**) about equal amounts of aniline-1- C^{14} (**[14]**) and aniline-2- C^{14} (**[15]**) were formed. More or less probable alternative



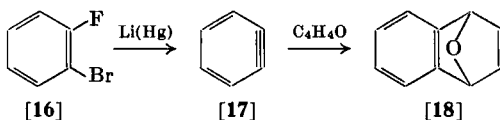
³ R. Huisgen and H. Rist, *Naturwissenschaften* **41**, 358 (1954); *Ann. Chem.* **594**, 137 (1955).

⁴ J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith, and C. W. Vaughan, *J. Am. Chem. Soc.* **75**, 3290 (1953).

interpretations were excluded by subsequent ingenious investigations.⁵⁻⁷

At the same time proof accumulated that arynes can be considered as real intermediates and not, e.g., as resonance structures in the activation complex of the transition state:

(a) Reactions were discovered wherein benzyne was "captured" by reagents which cannot generate it from the starting substance; e.g., the reaction of *o*-bromofluorobenzene (**16**) with lithium amalgam in the presence of furan yielded dihydronaphthalene-1,4-endoxide (**18**).⁸ Thus, **16** is transformed by lithium into benzyne (**17**) which then reacts as a dienophile with furan in a Diels-Alder addition (**17** → **18**).



(b) Quantitative experiments by Huisgen *et al.*⁹ on the competition of lithium piperidide and phenyllithium for benzyne originating from different halogenobenzenes show that in these reactions benzyne and not a complex of benzene and a halogen atom is an intermediate.

(c) In a medium containing no ionized reagent, benzyne was formed by heating *o*-benzenediazonium carboxylate (**19**) in the presence of furan (Stiles and Miller¹⁰). As in the experiment of Wittig and Pohmer described above, dihydronaphthalene-1,4-endoxide (**17**) was obtained.

(d) Finally, Berry *et al.*¹¹ demonstrated by flash photolysis the formation of gaseous benzyne, from solid *o*-benzenediazonium carboxylate (**19**), as a precursor of biphenylene (**20**).

Although neither benzyne nor any other aryne has been isolated, it appears from the foregoing that we are justified in considering these intermediates to be short-lived substances, the properties of which can be described by the series of resonance structures **17** and **21-23**.

⁵ J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Am. Chem. Soc.* **78**, 601 (1956).

⁶ G. E. Hall, R. Piccolini, and J. D. Roberts, *J. Am. Chem. Soc.* **77**, 4540 (1955).

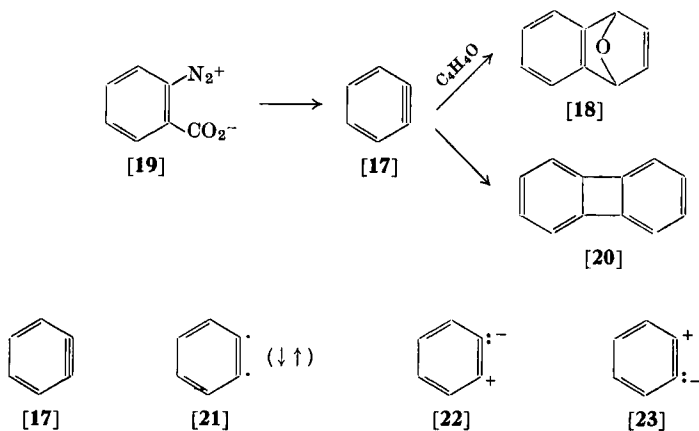
⁷ M. Panar and J. D. Roberts, *J. Am. Chem. Soc.* **82**, 3629 (1960).

⁸ G. Wittig and L. Pohmer, *Angew. Chem.* **67**, 348 (1955); *Chem. Ber.* **89**, 1334 (1956).

⁹ R. Huisgen, W. Mack, and L. Möbius, *Tetrahedron* **9**, 29 (1960).

¹⁰ R. M. Stiles and R. Miller, *J. Am. Chem. Soc.* **82**, 3802 (1960).

¹¹ R. S. Berry, G. N. Spokes, and R. M. Stiles, *J. Am. Chem. Soc.* **82**, 5240 (1960).



For discussions concerning their structure and further information on the generation and reactivity of arynes the reader is referred to a series of published reviews.^{12a-i}

Hetarynes can be expected to differ from carbocyclic arynes in several respects, i.e.:

- (1) There are usually isomers of an unsubstituted hetaryne.
- (2) Since unsubstituted hetarynes are usually asymmetric, their participation in a reaction can manifest itself in the occurrence of a rearrangement.
- (3) The properties of a hetaryne in which the $\text{C} \equiv \text{C}$ bond is adjacent to the hetero atom may differ considerably from those of its isomer(s).
- (4) The ratio of the amounts of isomeric addition products will depend on the orienting effect of the hetero atom in the nucleus.
- (5) The action of nucleophiles on a monosubstituted heterocyclic compound may generate isomeric hetarynes.
- (6) Heterocyclic compounds may show a higher tendency than carbocycles to react with nucleophiles according to the addition-elimination mechanism than via arynes.

¹² (a) G. Wittig, *Angew. Chem.* **69**, 245-251 (1957); (b) E. F. Jenny, M. C. Caserio, and J. D. Roberts, *Experientia* **14**, 349-354 (1958); (c) J. D. Roberts, *Chem. Soc. (London), Spec. Publ.* **12**, 115 (1958); (d) R. Huisgen and J. Sauer, *Angew. Chem.* **72**, 91-108 (1960); (e) R. Huisgen, in "Organometallic Chemistry" (H. Zeiss, ed.), Reinhold, New York, 1960; (f) J. F. Bunnett, *J. Chem. Educ.* **38**, 278-285 (1961); (g) H. Heaney, *Chem. Rev.* **62**, 81-97 (1962); (h) G. Wittig and H. Boos, *Angew. Chem.* **74**, 479-483 (1962); (i) J. Sauer, *Chem. Weekblad* **59**, 57-71 (1963).

These characteristic properties of hetarynes will be discussed in the section on pyridines, which have been investigated more extensively than other hetarynes.

This review covers the literature up to the beginning of 1963. Papers published before the era of aryne chemistry that merely give incidental information on reactions which might proceed via hetarynes are not included.

II. Azaarynes

A. PYRIDYNES

1. General

Whereas only one dehydrobenzene, benzyne, has been detected, two pyridynes are possible. Thus, the scheme we can write *ab initio* for the action of a nucleophile on the isomeric monosubstituted derivatives of pyridine involving 2,3- (26) and/or 3,4-pyridyne (31) is more complicated than that for the analogous reaction of the corresponding benzene derivative. The validity of this scheme can be checked using data available in the literature on reactions of halogenopyridines with potassium amide and lithium piperidide involving pyridynes.

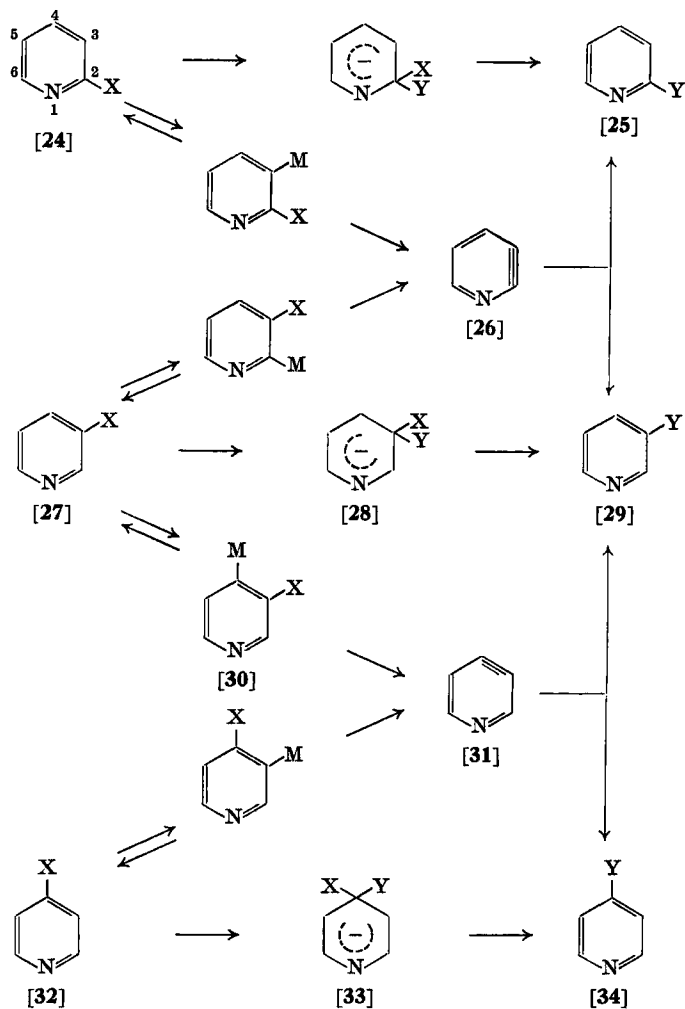
The first amination of a halogenopyridine involving a rearrangement was carried out by Levine and Leake¹³ in 1955 in an attempt to prepare 3-phenacylpyridine. When 3-bromopyridine (27, X = Br) was allowed to react with sodium amide in liquid ammonia in the presence of sodio-acetophenone, the reaction mixture obtained consisted chiefly of amorphous nitrogenous material from which only 10% of 4-aminopyridine (34, Y = NH₂) and 13.5% of 4-phenacylpyridine were isolated.

In 1961 a more extensive investigation of the amination of halogenopyridines with potassium amide (4 equivalents) in liquid ammonia at -33° was published (Pieterse and den Hertog^{14,15}). From the amination of 3-chloro (27, X = Cl), 3-bromo- (27, X = Br), and 3-iodo-pyridine (27, X = I) and the three corresponding 4-halogenopyridines (32, X = Cl, Br, I), total yields of 60–70% of mixtures of 3- (29, Y = NH₂) and 4-aminopyridine (34, Y = NH₂) were obtained. Gas chromatographic analyses of the reaction products showed that the composition of all reaction mixtures was the same and that the ratio of 3- (29, Y = NH₂) and 4-aminopyridine (34, Y = NH₂) was 1:2.

¹³ R. Levine and W. W. Leake, *Science*, **121**, 780 (1955).

¹⁴ M. J. Pieterse and H. J. den Hertog, *Rec. Trav. Chim.*, **80**, 1376 (1961).

¹⁵ M. J. Pieterse, Thesis, Amsterdam, The Netherlands, 1962.



2-Aminopyridine (**25**, Y = NH₂) was not detected in the reaction mixture.

The independence of the composition of the reaction products from the nature and position of the halogeno substituent clearly demonstrates that the amination of the isomeric 3- (**27**, X = Cl, Br, I) and 4-halogenopyridines (**32**, X = Cl, Br, I) proceeds exclusively via 3,4-pyridine (**31**). It is surprising that the 4-halogenopyridines did not

react according to the addition-elimination mechanism and that the 3-halogenopyridines yielded only 3,4-pyridyne and not a mixture of 2,3- (26) and 3,4-pyridyne (31).

Amination of the various four 2-halogenopyridines (24, X = F, Cl, Br, I) under analogous conditions gave 2-aminopyridine (25, Y = NH₂) as the sole reaction product in greater than 85% yield.¹⁴⁻¹⁶ The mechanism of these reactions is discussed in Section II, A, 3.

The reactions of various halogenopyridines with lithium piperidide and piperidine have been studied by Kauffmann and Boettcher.^{17, 18} By treating 3-bromo- (27, X = Br) or 3-chloropyridine (27, X = Cl) with lithium piperidide (2.2 equivalents) and piperidine (2.8 equivalents) in boiling ether, mixtures of 3- (29, Y = NC₅H₁₀) and 4-piperidinopyridine (34, Y = NC₅H₁₀) were obtained in 85-90% total yield. In both reactions the ratio of the 3- to 4-piperidino compounds was 48:52.¹⁹ Support for the hetaryne mechanism as the sole pathway for these reactions comes from the fact that increasing the amounts of lithium piperidide and piperidine to 5 and 10 equivalents, respectively, scarcely changed the composition of the reaction products. If addition-elimination had occurred concomitantly with reaction via the hetaryne, more of the 3-piperidino compound would have been formed, since the reconversion of the lithium intermediate 30 into 27 by piperidine would be accelerated by the enhancement of the concentration of this substance.

3-Fluoropyridine (27, X = F) was converted under the same conditions in over 90% yield into a mixture of 96% 3-piperidinopyridine (29, Y = NC₅H₁₀) and 4% 4-piperidinopyridine (34, Y = NC₅H₁₀). Comparison with the ratio (1:1) of reaction products from 3-chloro- and 3-bromo-pyridine formed via 3,4-pyridyne indicates that in this case no more than 8% of the starting substance reacts via the aryne and the remainder reacts via the intermediate addition product 28 (X = F, Y = NC₅H₁₀). The different behavior of 3-fluoropyridine (27, X = F) can be explained by assuming that, although the fluoro compound is transformed more easily than the other 3-halogenopyridines into the

¹⁶ R. J. Martens and H. J. den Hertog, *Rec. Trav. Chim.* **83**, 621 (1964).

¹⁷ T. Kauffmann and F. P. Boettcher, *Angew. Chem.* **73**, 65 (1961).

¹⁸ T. Kauffmann and F. P. Boettcher, *Chem. Ber.* **95**, 1528 (1962).

¹⁹ This finding is in agreement with a result obtained in 1958-59 by R. Huisgen and K. Herbig; i.e., in a reaction of 3,4-pyridyne with piperidine addition products were formed in a 52:48 ratio. See R. Huisgen, in "Organometallic Chemistry" (H. Zeiss, ed.), p. 78, Reinhold, New York, 1960.

lithium derivative **30** ($X = F$), lithium fluoride is eliminated very slowly. Thus, the greater part of **30** formed is reconverted by piperidine into starting material and little 3,4-pyridyne is produced, with the result that the rate of the addition-elimination reaction exceeds that of the hetaryne process.

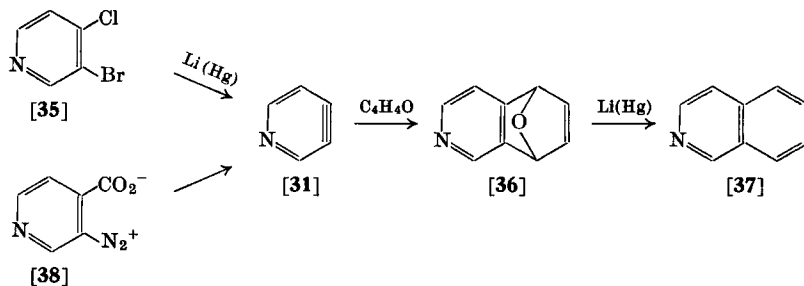
None of the 3-halogenopyridines yield 2-piperidinopyridine. This substance was obtained as the only product from the reaction of 2-fluoropyridine (**24**, $X = F$) with lithium piperidide under the same conditions in 97% yield. Finally, it was found that 4-chloropyridine (**32**, $X = Cl$) was converted in 95% total yield into a mixture of 0.4% of 3-piperidino- (**29**, $Y = NC_5H_{10}$) and 99.6% of 4-piperidino-pyridine (**34**, $Y = NC_5H_{10}$). Thus, in contrast to the amination with potassium amide, 4-chloropyridine reacts with lithium piperidide almost exclusively via the addition product **33** ($X = Cl$, $Y = NC_5H_{10}$).

The data described above give sound evidence for the existence of 3,4-pyridyne but do not indicate that 2,3-pyridyne occurs as an intermediate. The generation and reactivity of 3,4-pyridyne and some of its derivatives are discussed next. Section II, A, 3 deals with problems concerning 2,3-pyridyne.

2. 3,4-Pyridyne

3,4-Pyridyne is formed and reacts as a dienophile in reactions analogous to those described by Wittig and Pohmer⁸ and by Stiles and Miller¹⁰ in benzyne chemistry.^{17, 20}

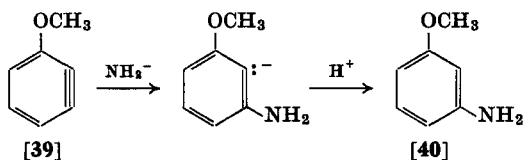
Shaking 3-bromo-4-chloropyridine (**35**) with lithium amalgam and furan gave a mixture from which isoquinoline (**37**) could be isolated in 14% yield; the endoxide (**36**) initially formed is deoxygenated by the amalgam. By heating 3-pyridinediazonium-4-carboxylate (**38**) in furan, the endoxide (**36**) could be isolated in greater than 60% yield.



²⁰ T. Kauffmann and F. P. Boettcher, *Chem. Ber.* **95**, 949 (1962).

Those reactions of halogenopyridines with potassium amide and lithium piperidide which proceed via 3,4-pyridyne form the 3- and 4-substituted pyridine derivatives in ratios of 1:2 and 1:1, respectively (see Section II, A, 1). It appears that the ring nitrogen atom has an orienting effect on these additions, but the quantitative divergence of the addition of ammonia and piperidine is not understood at present.

According to Roberts *et al.*²¹ the direction of addition of ammonia to 3-substituted benzyne might be predicted by considering the amide ion to add so as to provide the most favorable location of the negative charge with respect to the inductive effect of the orienting substituent. Thus, ammonia adds to 3-methoxybenzyne (**39**) producing chiefly *m*-aminoanisole (**40**).



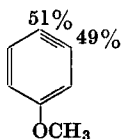
In addition reactions involving 4-substituted benzyne the situation is more complicated, because the inductive effects of the substituents are weaker and the conjugative electrical effects become relatively important. 4-Methoxybenzyne (**41**) was found to give about equal amounts of *p*- and *m*-aminoanisole, and 4-fluorobenzyne (**42**) yielded *p*- and *m*-aminofluorobenzene in a ratio of 80:20 in experiments which were said to represent qualitatively the proportions of isomers formed. Data on the addition of piperidine to 4-substituted benzyne are available from investigations by Huisgen and Herbig.²² The ratio of products from 4-methoxybenzyne (**43**) was found to be ~ 1:1 again, but 4-fluorobenzyne (**44**) gave *para* and *meta* isomers in a ratio of 67:33. When we see that 4-dimethylaminobenzyne (**45**) gives *p*- and *m*-derivatives in a ratio of 35:65, it is obvious that at present the mode of addition of ammonia and piperidine to 3,4-pyridyne cannot be correlated with results in benzyne chemistry.

Ethoxy derivatives of 3,4-pyridyne were found to play a role in the amination of bromoethoxypyridines with potassium amide in liquid

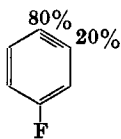
²¹ Cf. J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, and D. A. Semenow, *J. Am. Chem. Soc.* **78**, 611 (1956).

²² R. Huisgen and K. Herbig, *Chem. Ber.* in press; cf the review cited in reference 12d, p. 106.

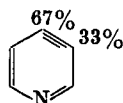
ammonia.^{14, 15, 23} In these reactions bromoethoxypyridines are converted quantitatively within minutes into aminoethoxypyridines, and the addition ratios are shown in structures 46–48.



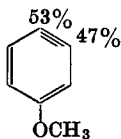
[41]



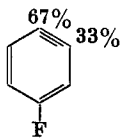
[42]



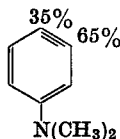
Isomer distribution on addition of ammonia.



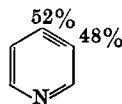
[43]



[44]

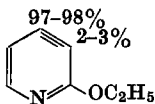


[45]

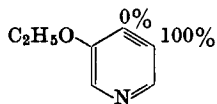


Isomer distribution on addition of piperidine.

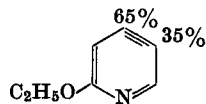
2-Ethoxy-3,4-pyridyne (46) is involved in the amination of 3- and 4-bromo-2-ethoxypyridine, and mixtures of aminoethoxypyridines of the same composition are formed in both reactions. Thus, from 4-bromo-2-ethoxypyridine only the 3-hydrogen atom, situated between the bromine and ethoxyl groups (and not the 5-hydrogen atom) is abstracted. Pyridyne 47 is an intermediate in the amination of 4- and 5-bromo-3-ethoxypyridine. In the last-mentioned substance, just as in 5- (or 3-)bromopyridine, only the 4-hydrogen atom, and not the 2-hydrogen atom, is abstracted. The amination of 3-bromo-6-ethoxypyridine proceeds via 6-ethoxy-3,4-pyridyne (48); again the 2,3-pyridyne derivative is not formed.



[46]



[47]



[48]

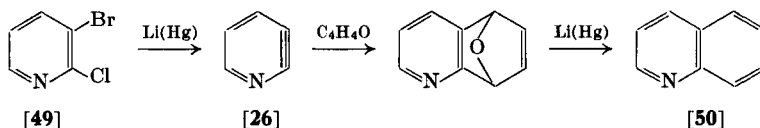
The addition ratios observed for 46 and 47 can be associated with a *meta*-orienting effect of the ethoxy group, analogous to that observed

²³ H. J. den Hertog, M. J. Pieterse, and D. J. Buurman, *Rec. Trav. Chim.* **82**, 1173 (1963).

for 3-methoxybenzyne. It is remarkable that not even a trace of the 4-amino compound is formed from **47**. Evidently the orienting effect of the ethoxy group surpasses entirely that of the remote nitrogen atom. In **48**, however, both the ring nitrogen atom and the ethoxy group occupy positions remote from the "triple bond," and the addition ratio²⁴ (2:1) is the same as for 3,4-pyridyne. The ring nitrogen atom seems to promote the introduction of the amino group into position 4 since the amination of 4-methoxybenzyne (**41**) with potassium amide yields *m*- and *p*-amino compounds in equal amounts.

3. 2,3-Pyridyne

2,3-Pyridyne (**26**) has been shown to exist by trapping it with furan. It must be considered to be an intermediate in the reaction of 3-bromo-2-chloropyridine (**49**) with lithium amalgam because in the presence of furan a small amount ($\sim 2\%$) of quinoline (**50**) is formed.²⁵



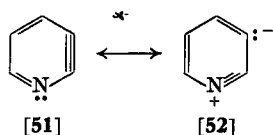
Why, then, was 2,3-pyridyne not found to play a role in the amination of 2- and 3-halogenopyridines?

It has been proved that 2,3-pyridyne is not generated in the amination of any 3-halogenopyridine (**27**, X = F, Cl, Br, I) (see Section II, A, 1). An explanation for its absence in mixtures formed by reacting 3-chloropyridine (**27**, X = Cl) with lithium piperidide in piperidine has been given by Kauffmann and Boettcher.¹⁸ It is supposed that in this reaction the metallation, yielding 3-chloro-2-lithiopyridine, really takes place, but that the negative charge at C-2, resulting from polarization of the lithium-carbon bond, is weakened by the inductive effect of the ring nitrogen atom and, therefore, does not weaken the neighboring chlorine-carbon bond. Thus lithium chloride is not split off and the formation of 2,3-pyridyne does not occur. Protolysis by piperidine regenerates 3-chloropyridine (**27**, X = Cl).

²⁴ The formation of 3- and 4-amino-6-ethoxypyridine in a 1:5 ratio in this reaction (reported in references 14 and 15) is not correct due to an error in the method used for the gas chromatographic analysis (cf. reference 23).

²⁵ R. J. Martens and H. J. den Hertog, *Tetrahedron Letters* No. 15, 643 (1962).

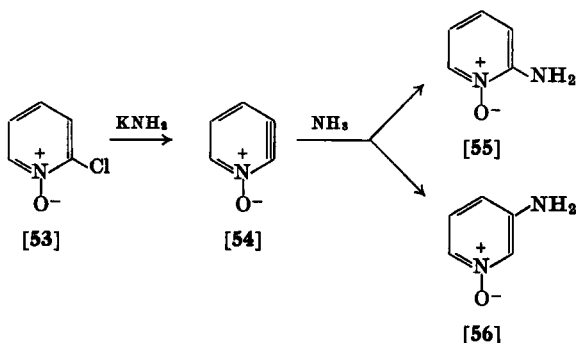
It should be stated, however, that there is no sound proof that 2,3-pyridyne is not involved as an intermediate in the amination of 2-halogenopyridines (**24**, X = F, Cl, Br, I). No rearrangement has been observed and it has therefore been assumed that these reactions proceed according to the addition-elimination mechanism only. There is no reason, however, to suppose that 2,3-pyridyne should not be formed from 2-halogenopyridines. The arguments given to show that it does not originate in the amination of 3-halogenopyridines do not hold in this case. The argument used against the formation of 2,3-pyridyne is that in the amination of 2-halogenopyridines no 3-substituted product is produced, whereas the inductive effect of the hetero nitrogen atom should favor the addition of the amide ion to C-3 of 2,3-pyridyne. It is doubtful whether this orientation rule can be applied here, for although it comes from benzyne chemistry, as is explained in Section II, A, 2, it is only valid for 3-substituted benzyne such as 3-methoxy-benzyne (**39**). On comparison of the resonance structures of 2,3-pyridyne (**51** and **52**) and 3-methoxybenzyne (**39**), these intermediates do not appear to have analogous constitutions. Thus, we cannot predict the mode of addition to 2,3-pyridyne from data obtained in experiments on the orientation of the products from the amination of 2- and 3-substituted halogenobenzenes.^{25a}



While awaiting the results of tracer experiments, the present authors prefer to desist from assuming that the route from **24** to **25** via the addition product shown is the only pathway followed in the amination of 2-halogenopyridines. This is the more so since it seems probable that in the experiments described below *derivatives* of 2,3-pyridyne occur as intermediates.

The amination of 2-chloropyridine-*N*-oxide (**53**) with potassium amide in liquid ammonia yielded a mixture of 2-(**55**) and 3-aminopyridine-*N*-oxide (**56**) in 5–10% total yield.¹⁶ This rearrangement might be explained by an aryne mechanism involving 2,3-pyridyne-*N*-oxide (**54**).^{25b} Since the structure of **56**, with its quaternary nitrogen atom, is more analogous to that of 3-methoxybenzyne (**39**) than to that of 2,3-pyridyne (**26**), an orientation effect directing the amide ion to C-3 can be expected here.

^{25a} Recently H. L. Jones and D. L. Beveridge have presented molecular orbital calculations on the electronic structure of 2,3-pyridyne explaining the exclusive formation of 2-aminopyridine from this intermediate [*Tetrahedron Letters* No. **24**, 1577 (1964)].



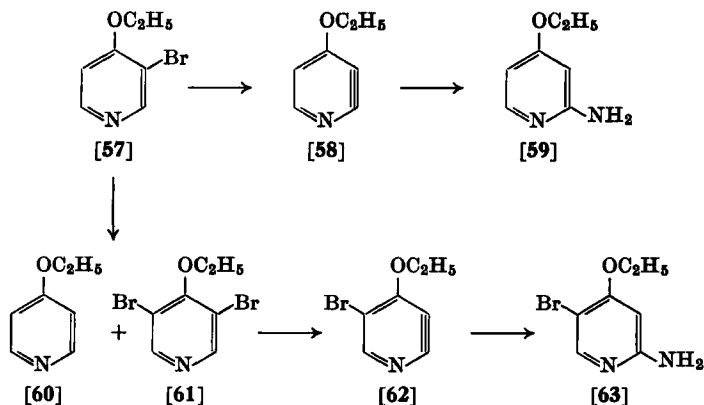
The amination reactions of substituted bromopyridines, which might proceed via derivatives of 2,3-pyridyne, have also been investigated. Reactions of some derivatives of 3-bromopyridine were studied in which the formation of 2,3-pyridyne derivatives was favored by introduction of a substituent in the 4-position, thus preventing the competing formation of 3,4-pyridyne. 3-Amino-4-picoline, when reacted with potassium amide in liquid ammonia, gave some 2,4-diaminopyridine in a very slow reaction; 3-bromo-4-picoline was transformed at a somewhat higher rate into the 2-amino derivative again.^{25c} 3-Bromo-4-ethoxypyridine (57) was converted in a fast reaction; 2-amino-4-ethoxypyridine (59) was formed in a yield of 55–60% when 57 was treated with the reagent for 5 minutes only.^{14, 15} Thus, it appears that the amide ion is added to C-2 of the various derivatives of 2,3-pyridyne used, independently of the character of the substituent occupying the 4-position.^{25c} The amination of 3-bromo-4-ethoxy-pyridine (57) is more complicated, however, because 2-amino-5-bromo-4-ethoxypyridine (63) and 4-ethoxypyridine (60) were also formed in yields of 15–20% and 25%, respectively. In the mixture resulting from an amination reaction of short duration with a slight excess of potassium amide, some 3,5-dibromo-4-ethoxypyridine (61) was detected, and this compound was converted by subsequent amination into 2-amino-5-bromo-4-ethoxypyridine (63). The reaction scheme 57–63 was proposed to explain these observations.^{14, 15, 26}

In 57 a bromine migration possibly competes with the generation of 4-ethoxy-2,3-pyridyne (58), induced by the abstraction of a hydrogen ion from C-2 of 57 (cf. the isomerization of 1,2,4-tribromobenzene to

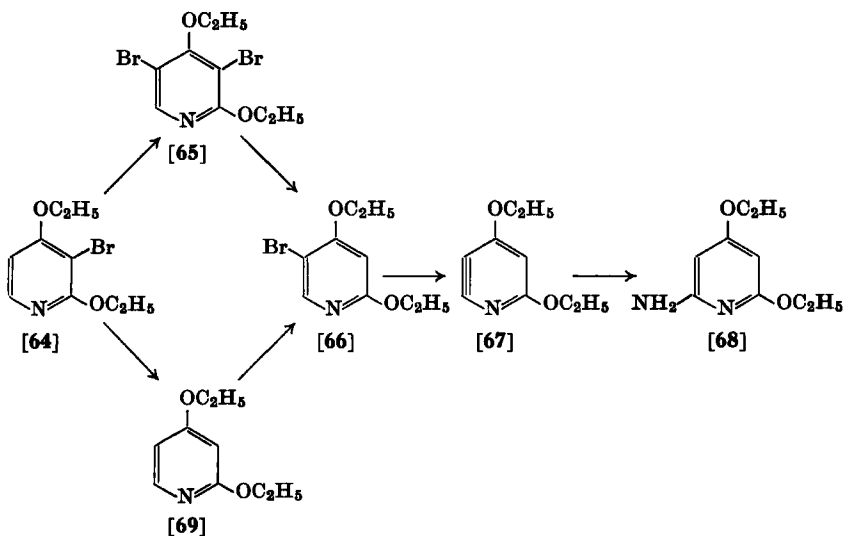
^{25b} This result has been confirmed by T. Kato, T. Niitsuma, and N. Kusaka, *Yakugaku Zasshi* **84**, 432 (1964); *Chem. Abstr.* **61**, 4171 (1964).

^{25c} R. J. Martens and H. J. den Hertog, unpublished results.

²⁶ M. J. Pieterse and H. J. den Hertog, *Rec. Trav. Chim.* **81**, 855 (1962).



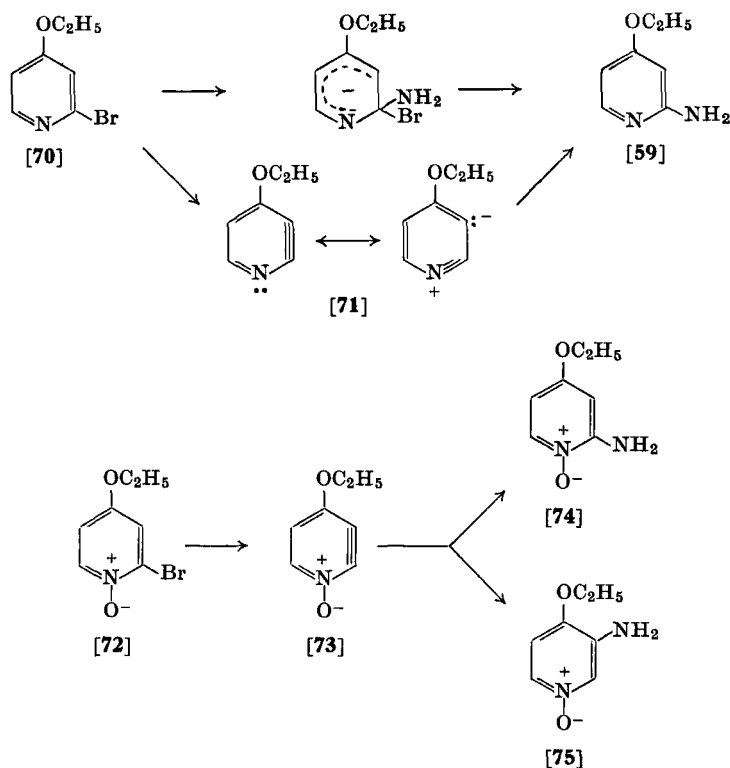
1,3,5-tribromobenzene through the action of potassium amide in liquid ammonia, reported by Wotiz and Huba²⁷ and discussed recently by Moyer and Bunnett²⁸). Thus, some of the 3-bromo-4-ethoxypyridine (57) is converted into a mixture of the dibromo compound 61 and 4-ethoxypyridine (60), and formation of 63 may proceed via a second arylene 62. This bromine migration must be taken into consideration when trying to explain such curious reactions as the *para*



²⁷ J. H. Wotiz and F. Huba, *J. Org. Chem.* **24**, 595 (1959).

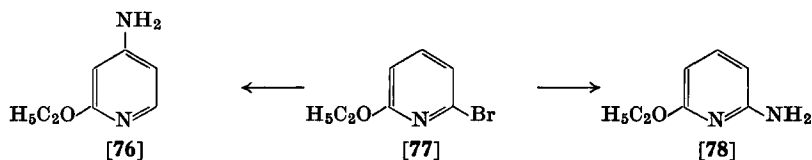
²⁸ C. E. Moyer, Jr., and J. F. Bunnett, *J. Am. Chem. Soc.* **85**, 1891 (1963).

rearrangement observed during the amination of 3-bromo-2,4-diethoxypyridine (**64**). This substance cannot react via an aryne and reaction via an addition product is unlikely in the 3-position. When **64** was treated with potassium amide in liquid ammonia, 6-amino-2,4-diethoxypyridine (**68**) was formed in $\sim 50\%$ yield. Analysis of the mixture formed in an amination reaction which was interrupted after some minutes elucidated the course of the reaction. 5-Bromo-2,4-diethoxypyridine (**66**), possibly formed via **65**, was detected together with some 2,4-diethoxypyridine (**69**) and bromination product(s) of **68**. Thus, a derivative of 2,3-pyridyne (**67**) seems to play a role in this reaction.^{15, 26}



Amination of derivatives of 2-bromopyridine gave, just as did the same reaction of 2-bromopyridine itself, no decisive answer concerning the mechanism of these processes, except that 2-bromo-3-ethoxy-

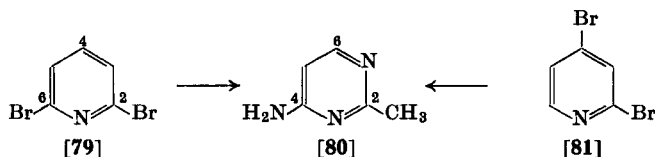
pyridine is converted rapidly into 2-amino-3-ethoxypyridine, and this reaction cannot proceed via an aryne.^{14, 15} 2-Bromo-4-ethoxypyridine (70) and 2-bromo-5-ethoxypyridine give only the 2-amino compounds and may therefore react according to the addition-elimination mechanism, but it is rather intriguing that 2-bromo-4-ethoxypyridine-*N*-oxide (72) gives a mixture of both 2- (74) and 3-amino-4-ethoxypyridine-*N*-oxide (75) in ~15% total yield.¹⁶ It seems probable that the last reaction proceeds via 4-ethoxy-2,3-pyridyne-*N*-oxide (73) and that addition to this intermediate is directed by the inductive effects of the ethoxy and *N*-oxide groups to the 2- and 3-positions, respectively. It is not impossible that the amination of 2-bromo-4-ethoxypyridine (70) to give 2-amino-4-ethoxypyridine (59) occurs at least partially via 4-ethoxy-2,3-pyridyne (71), with the amide ion being directed exclusively to the 2-position. An unexpected result was obtained in the amination of 2-bromo-6-ethoxypyridine (77). Here a fast reaction occurred to yield a mixture of 80–85% of 2-amino-6-ethoxypyridine (78) and 15–20% of 4-amino-6-ethoxypyridine (76).^{14, 15} No by-products were formed in contrast to the amination of 3-bromo-4-ethoxypyridine (57) and 3-bromo-2,4-diethoxypyridine (64).



Attempts to get more information on this interesting *meta*-rearrangement by choosing derivatives of 2-bromopyridine containing various substituents in the 6-position for the starting material led to a remarkable result. Whereas 2-bromo-6-picoline gave a mixture of 2- and 4-amino-6-picoline (in a ratio of 60:1) in 25% total yield together with a resinous mass,¹⁵ 2,6-dibromopyridine (79) was converted into a pyrimidine, i.e. 4-amino-2-methylpyrimidine (80), in ~20% yield.²⁹ The same pyrimidine was obtained from 2,6-dichloropyridine and, in small amount, also from 2,4-dibromopyridine (81). The course of the

²⁹ Investigation by H. J. den Hertog, H. C. van der Plas, M. J. Pieterse, and J. W. Streef; cf. H. J. den Hertog, Abstr. A, XIXth Intern. Congr. Pure Appl. Chem., p. 279 (1963). H. C. van der Plas and B. Haase [*ibid.*, p. 279 (1963)] describe an analogous conversion of 4-chloro-2-methylpyrimidine into 2,4-dimethyl-*s*-triazine.

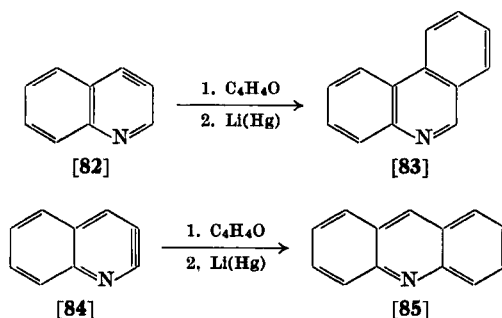
conversion of these dihalogenopyridines into derivatives of pyrimidine has not been elucidated, and these findings do not help to explain the mechanism of the *meta* substitution observed in the amination of 2-bromo-6-ethoxypyridine (**77**). A comparison of formulas **79** and **80** shows that in the reaction of 2,6-dibromopyridine with potassium amide an amide ion reacts at the 4-position, but, since no further data are available, it is still uncertain whether a pyridyne is involved in these curious reactions of 6-substituted derivatives of 2-halogenopyridines.



B. QUINOLYNES

Quinolynes are generated and behave analogously to pyridynes.^{30, 31}

The reaction of 3-bromo-4-chloro- and 3-bromo-2-chloro-quinoline with lithium amalgam in the presence of furan gives phenanthridine (**83**, 9% yield) and acridine (**85**, ~ 0.1% yield), respectively, via 3,4- (**82**) and 2,3-quinolyne (**84**).



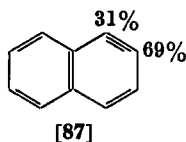
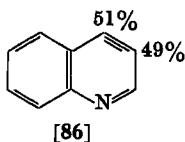
The four 3-halogenoquinolines were allowed to react with lithium piperidide and piperidine (molar ratio 1:2.2:2.8) in boiling ether. The chloro, bromo, and iodo compound gave, in 45–60% total yield, mixtures of 3- and 4-piperidinoquinoline of the same composition

³⁰ T. Kauffmann, F. P. Boettcher, and J. Hansen, *Ann. Chem.* **659**, 102 (1962).

³¹ T. Kauffmann and K. Udluft, *Angew. Chem.* **75**, 89 (1963).

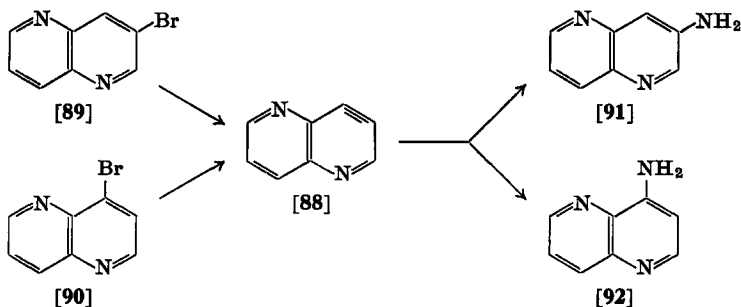
(ratio 49:51); 3-fluoroquinoline gave only 3-piperidinoquinoline in 75% yield. Thus, just as in pyridine chemistry, there is a difference in the reactivity towards lithium piperidide and piperidine of the fluoro compound and the other halogeno compounds. The first substance reacts according to the addition-elimination mechanism and the latter compounds via 3,4-quinolyne only. The occurrence of the aryne mechanism is confirmed by the fact that increasing the amount of piperidine in the reaction mixture does not change the ratio of the reaction products (cf. Section II, A, 1). No 2-piperidinoquinoline was detected in any of the experiments.

In the addition of piperidine to 3,4-quinolyne, the orienting effect of the nitrogen atom manifests itself in bringing the ratio of the 3- and 4-substituted derivatives formed to 49:51 (cf. **86**), whereas the ratio is 69:31 in the case of 3,4-naphthalene (cf. **87**).



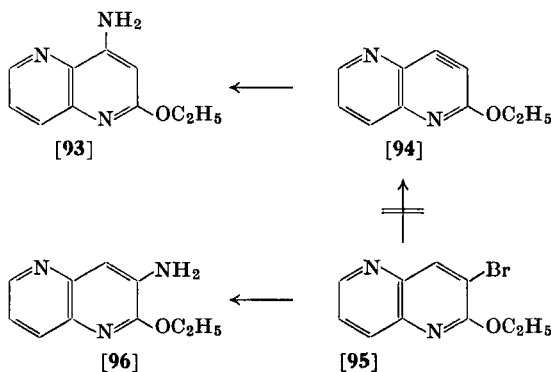
C. 1,5-NAPHTHYRIDINES

There is evidence for 1,5-naphthyridyne-3,4 (**88**), but none for 1,5-naphthyridyne-2,3, from the results of the amination of 2-, 3-(**89**), and 4-bromo-1,5-naphthyridine (**90**) with potassium amide in liquid ammonia.³² Both **89** and **90** yield mixtures of 3- (**91**) and 4-amino-1,5-naphthyridine (**92**) but no 2-amino-1,5-naphthyridine. It therefore appears that 1,5-naphthyridyne-3,4 (**88**) is an intermediate



³² W. Czuba, *Rec. Trav. Chim.* **82**, 997 (1963).

in both aminations. However, the ratios of the 3- and 4-amino compounds (**91** and **92**) in the reaction mixtures are not the same: the product ratio from **89** is 6:1 and from **90** it is 3.5:1. Thus, in one of the aminations, or in both, the addition-elimination reaction proceeds concurrently with the aryne mechanism. One hesitates, however, to assume that it is largely the 4-bromo compound (**90**) which reacts by addition-elimination in view of the unexpected result that the amination of 3-bromo-2-ethoxy-1,5-naphthyridine (**95**) with potassium amide in liquid ammonia proceeds without rearrangement: only the 3-amino compound **96** was obtained (fair yield). From this it might be concluded that the 3-bromo derivative (**89**) tends to react according to the addition-elimination mechanism. If 3-bromo-2-ethoxy-1,5-naphthyridine (**95**) had reacted via **94**, some of the 4-amino derivative (**93**) should have been formed due to the *meta*-orienting effect of the ethoxy group.

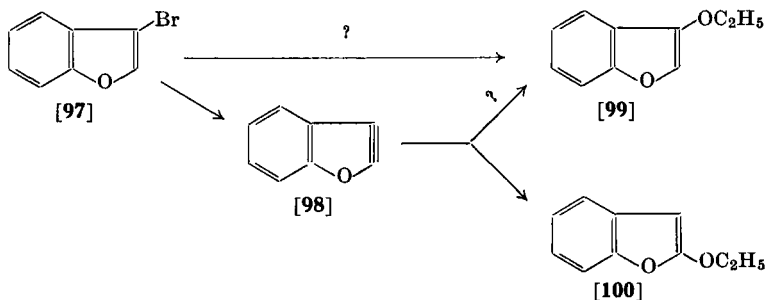


The amination of 2-bromo-1,5-naphthyridine also proceeds without rearrangement to yield 2-amino-1,5-naphthyridine (up to 80%) together with 1,5-naphthyridine (10%) and a substance ($C_8H_8N_4$, 10% yield) of unknown structure as by-products. Thus, here also it remains uncertain whether a 2,3-aryne is an intermediate.

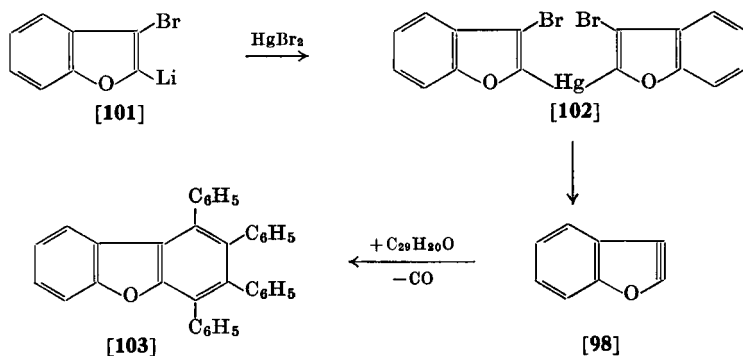
III. Oxaarynes

Apparently only one hetaryne containing oxygen as a hetero atom, 2,3-dehydrocoumarone (**98**), has been described thus far. It was formulated by Stoermer and Kahlert² as an intermediate containing a "triple bond" in its hetero ring system as early as 1902 and was probably the first aryne mentioned in the literature of organic

chemistry. It was assumed to be involved in reactions occurring during the heating of 3-bromocoumarone (**97**) with sodium ethylate under pressure, from which 2-ethoxy- (**100**) and 3-ethoxy-coumarone (**99**) together with other products were obtained. Stoermer and Kahler² tried to isolate an intermediate substance with acetylenic



properties, which they thought was formed from **97** by abstraction of hydrogen bromide and which would be able to add alcohol analogously to phenylacetylene. Being unsuccessful in this attempt they ascribed their failure to the instability of the unsaturated compound, but supposed a curious irritating smell, which was always observed when opening the autoclave, to come from a small amount of the intermediate still present in the reaction mixture. Nevertheless, they published their daring mechanism with the reservation that part of the 2-ethoxycoumarone produced might result from direct replacement. Quite recently this legendary aryne was again generated, and proved to have dienophilic properties, by Wittig and Boos.^{32a} The aryne **98** was obtained from 3-bromo-2-lithiocoumarone (**101**), a comparatively stable substance [cf. the supposed stability of 3-chloro-2-lithiopyridine

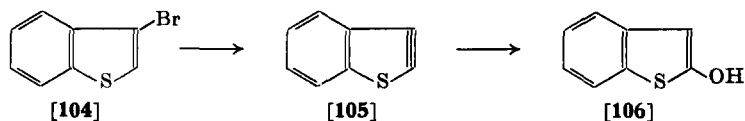


^{32a} G. Wittig and H. Boos (see the paper cited in reference 12h).

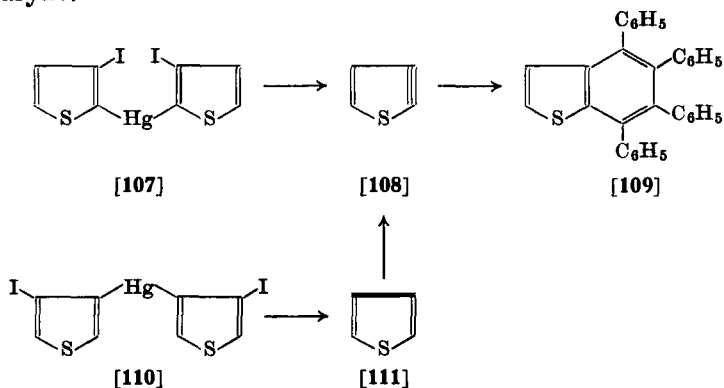
(Section II, A, 3)], by conversion into the mercury compound **102** and subsequent heating. Aryne **98** was trapped with tetracyclone and the product (**103**) was formed in 70% yield.

IV. Thiaarynes

Two hetarynes containing sulfur as a hetero atom have been mentioned in the literature. The first thiaaryne, 2,3-thianaphthyne (**105**), may have been handled by Komppa and Weckman³³ in 1933. On heating 3-bromothianaphthene (**104**) with a solution of potassium hydroxide in ethanol at 200°, a reaction mixture was obtained consisting of unchanged starting material (4%), thianaphthene (65%), and 2-hydroxythianaphthene (**106**, 15%). The course of the reaction



was described as a primary formation of 3-hydroxythianaphthene and a rearrangement of this substance "*in statu nascendi*." This reaction is analogous to the reaction of 3-bromocoumarone (**97**) with sodium ethylate. If both processes are really examples of aryne chemistry, they illustrate the addition of a nucleophile to the 2-position of a 2,3-hetaryne.



The second thiaaryne is the 2,3-hetaryne derived from thiophene (**108**). It was obtained by Wittig and Wahl³⁴ by heating bis-(3-

³³ G. Komppa and S. Weckman, *J. Prakt. Chem.* **138**, 109 (1933).

³⁴ G. Wittig and V. Wahl, *Angew. Chem.* **73**, 492 (1961).

iodothieryl-2)-mercury (107) and trapped with tetracyclone, the tetraphenylthianaphthene (109) being formed in 9% yield (cf. the analogous reaction involving the 2,3-hetaryne derived from coumarone described in Section III. Curiously enough, bis-(3-iodothieryl-4)-mercury (110), when heated with tetracyclone, was reported to give the same tetraphenylthianaphthene (109) as its isomer (107). Thus, in this reaction the hetaryne 108 seems to be formed by isomerization of the less stable 3,4-dehydro compound 111 which is generated initially.

V. Note Added in Proof

As might be expected, hetaryne chemistry has been growing at an increasing rate since this review was written. When reading the proof we felt inclined to summarize the latest developments which have come to our attention.

The occurrence of several new hetarynes has been indicated by rearrangements observed. 4,5-Pyrimidyne was shown to be involved as an intermediate in the conversion of 5-bromopyrimidine with piperidine³⁵; 2-methyl-4,5-pyrimidyne in the reaction of 5-chloro-2-methylpyrimidine with sodium amide in liquid ammonia³⁶; and a series of 6-substituted derivatives of 4,5-pyrimidyne when reacting the 5-bromo compounds of 6-amino-, 6-*t*-butyl-, 6-dimethylamino-, 6-hydroxy-, 6-methoxy-, 6-methyl-, and 6-phenyl-pyrimidine with potassium amide in liquid ammonia.³⁷ 1-Methyl-2-phenyl-4,5-pyridazyne-dion-3,6 was generated when treating the 4-chloro derivative of the corresponding pyridazine with piperidine or sodium methylate.³⁸ The following new bicyclic hetarynes have been reported: 3,4-isoquinolyne³⁹ and 3,4-dehydrocoumarin,³⁵ formed by the action of piperidine on 4-bromoisoquinoline and 3-bromocoumarin, respectively, and possibly *N*-methyl-2,3-dehydroindole, produced by heating bis-(*N*-methyl-3-chloroindolyl-2)mercury.⁴⁰

The existence of some curious intermediates related to hetarynes has

³⁵ T. Kauffmann, J. Hansen, K. Udluft, and R. Wirthwein, *Angew. Chem.* **76**, 590 (1964).

³⁶ T. Schwan and H. Tieckelmann, *J. Org. Chem.* **29**, 941 (1964).

³⁷ H. C. van der Plas and G. Geurtsen, *Tetrahedron Letters* No. **31**, 2093 (1964); *Rec. Trav. Chim.* in press.

³⁸ T. Kauffmann and A. Risberg, *Tetrahedron Letters* No. **22**, 1459 (1963).

³⁹ Result of T. Kauffmann and J. Hansen, mentioned in reference 38.

⁴⁰ G. Wittig, *Pure Appl. Chem.* **7**, 180 (1963).

been discussed; i.e., of 1,2-dehydropyridinium, a cation which might be formed during the thermal decomposition of a base resulting from the reaction of 2-hydrazinopyridine with thionyl chloride⁴¹ and, from a theoretical point of view, of 2,6-dehydropyridine, a feasible intermediate in the amination of a 3,5-disubstituted pyridine.^{25a}

In an extensive investigation of the behavior of halogeno-pyridines and -quinolines towards potassium amide in liquid ammonia, tendencies to react according to the hetaryne type and other mechanisms were compared.⁴²⁻⁴⁴ The following results may be mentioned. 3-Fluoropyridine does not react via 3,4-pyridyne, but yields fluoro derivatives of 4,4'- and 2,4'-bipyridine.⁴² 3,6-Dibromopyridine is converted first into 6-bromo-3,4-pyridyne and not into 6-amino-3-bromopyridine.⁴³ 2-Bromoquinoline yields 2-methylquinazoline together with 2-aminoquinoline.⁴⁴

A new example of the reactivity of 3,4-pyridyne as a dienophile was reported (the conversion by cyclopentadiene³⁵) and a remarkable orienting effect of the amino group on the addition of ammonia to the triple bond in amino derivatives of 3,4-pyridyne,⁴⁴ e.g., the addition of the amide ion to C-4 in 5-amino-3,4-pyridyne.⁴⁵

Finally, the elimination-addition mechanism has been proposed to explain the course of the well-known Tschitschibabin reaction,⁴⁶ but this extension of hetaryne chemistry has been rightly objected to by several authors.⁴⁷⁻⁴⁹

⁴¹ T. Kauffmann and H. Marhan, *Chem. Ber.* **96**, 2519 (1963).

⁴² R. J. Martens and H. J. den Hertog, *Tetrahedron Letters*, in press.

⁴³ J. W. Streif and H. J. den Hertog, *Rec. Trav. Chim.*, in press.

⁴⁴ H. J. den Hertog and D. J. Buurman, *Rec. Trav. Chim.*, in press.

⁴⁵ Cf. the formation of *o*-diaminobenzene from *m*-aminobromobenzene and of *m*-diaminobenzene from *p*-aminobromobenzene by the action of potassium amide in liquid ammonia (unpublished result of G. B. R. de Graaff, W. C. Melger, and H. J. den Hertog).

⁴⁶ L. S. Levitt and B. W. Levitt, *Chem. Ind. (London)* 1621 (1963).

⁴⁷ G. C. Barrett and K. Schofield, *Chem. Ind. (London)* 1980 (1963).

⁴⁸ R. A. Abramovitch, F. Helmer, and J. O. Saha, *Chem. Ind. (London)* 659 (1964).

⁴⁹ Y. Ban and T. Wakamatsu, *Chem. Ind. (London)* 710 (1964).

Reactivity of Azine, Benzoazine, and Azinoazine Derivatives with Simple Nucleophiles

ROBERT G. SHEPHERD and JAMES L. FEDRICK

*Lederle Laboratories Division, American Cyanamid Company
Pearl River, New York*

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I. Introduction

A. PURPOSE AND SCOPE

1. Purpose

The relative reactivity of different positions in azines towards nucleophiles is an interesting problem which has not been solved although there is agreement on certain general features. We endeavor

here to arrive at and interpret a fundamental reactivity pattern of azines and to point out general principles or the need to establish them. Kinetic work on nucleophilic substitution of heteroaromatics is limited, so we have taken carboaromatic studies as part of the basis for postulating the behavior of azines, keeping in mind the theoretical consequences of important differences between the two. Extensive experimental work of Bunnett, Chapman, Miller, and their co-workers has done much to raise to a proper level the appreciation of *nucleophilic* substitution of aromatic compounds during the past decade. Nevertheless, a wide range of challenging questions and of uninvestigated types of compounds still remains.

Properly included in the category of nucleophilic substitution are certain reactions, e.g., various hydrolyses, thionations, and oxo-into-halo conversions,¹ which are often left unclassified. As Ingold^{2a} has pointed out, one does not need to know the detailed mechanism of a process to classify it. Inclusion of these reactions helps to demonstrate the great significance of nucleophilic substitution in heterocyclic chemistry. Addition reactions leading to dihydro-type compounds are not covered in this review, although many such reactions are closely related to nucleophilic substitutions in that they involve similar activation for nucleophilic attack and proceed through analogous intermediate complexes.

The term "aromatic" will be used in a *strict* non-historical sense to mean possessing a cyclic π -electron system (6 and 10 electrons for the mono- and bi-cyclic rings discussed in this review). Heteroaromatic compounds, like carboaromatics, have widely different degrees and types of electronic dissymmetry and polarizability. Consequently, their reactivity varies tremendously with any one reagent and their relative reactivity changes drastically with the type of reagent. In this sense, aromatic compounds show differences in reactivity but not in aromaticity. The virtues of this *qualitative* concept of aromaticity and the pitfalls of trying to use it as a quantitative concept in modern context have been ably presented by Peters³ and by Balaban and Simon.⁴

Insofar as they relate to the main theme of the relative reactivity of different rings and ring-positions, we shall discuss the role of the leaving group, mutual activation or deactivation by leaving groups and other substituents, activation due to cationization of a ring-nitrogen, certain aspects of hydrogen bonding, variations due to the nature of the nucleophile, specific "ortho effects," cyclic transition

states, entropy of activation effects, and the influence of different positions of annulation of a second aromatic ring. Activation by an azine-nitrogen is determined by the number and orientation of sp^2 -hybridized ring-nitrogens. When the leaving group in a bicyclic azine is in the ring adjacent to that of an activating nitrogen atom, activation is reduced by transmission factors which are clearly different for activation by induction and by resonance, and which vary further in specific ways with ring-position. Combinations of all these effects generally lead to predictable alterations of the fundamental reactivity pattern, provided the orientation of each effect is considered with respect to the ring-nitrogens as well as to the leaving group. Kinetic data are available for ten of the older ring systems, but, in many others, indications of minimal conditions required for displacement are not even available. Where possible, the known preparative nucleophilic substitutions are used merely as general evidence of reactivity of the ring and its various positions, and relative reactivity is predicted on the basis of the more definitive studies on other azines.

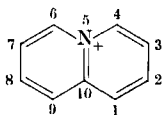
Each section begins with a summary and discussion of general effects followed by illustration of the generalizations by specific examples. This arrangement prepares the reader for what he is about to encounter and facilitates later use of the sections for reference.

2. Scope

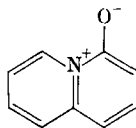
Monocyclic azines containing one to five nitrogen atoms comprise 11 ring systems with 19 positions of *different* orientation. In bicyclic azines without nitrogen bridges (excluded throughout), there are two possible monoazines having 14 different ring-positions, 10 diazines with 42 positions, 14 triazines with 70 positions, 22 tetrazines with 70 positions, 14 pentazines with 42 different ring-positions, 10 hexazines with 14 positions, and two bicyclic heptazines with 2 positions. Forty-two of these 85 possible ring systems (a total of 273 ring-positions with different orientation) are known in aromatic form through the 1963 *Chemical Abstracts* and in the current literature through early 1964. No nucleophilic displacements have been reported for 7 of the 42 known azine systems.

The exclusion of nitrogen-bridged bicyclic azines is purely arbitrary since the work^{5,6} on such azinoazines with a 10 π -electron system (and the necessarily accompanying quaternary nitrogen-bridgehead atom) shows the activation expected of other aromatic azinium

compounds. The quinolizinium cation (**1**) is aromatic as judged from its ultraviolet absorption spectrum which is very similar to those of

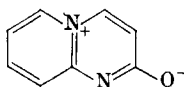


[1]

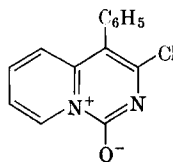


[2]

isoquinoline and quinoline. Activation for nucleophilic substitution would be expected at the 2-, 4-, 5-, and 7-positions in **1**. Good reactivity is demonstrated by the displacement⁶ of a 4-methylthio group by diethyl malonate anion and by the zwitterion from 1,4-dimethylquinolinium cation. The spectrum and stability of 4-quinolizino⁷ (**2**) and of the pyridopyrimidinone⁸ **3** indicate that these compounds exist in the aromatic zwitterionic structures shown in **2** and **3**. The related 3-chloropyridopyrimidin-1-one **4** undergoes nucleophilic substitution⁹ with alkoxides, alkylamines, and thiourea to form the corresponding 3-alkoxy, 3-alkylamino, and 3-isothiuronium derivatives.



[3]



[4]

The salient features of the reactivity pattern of azines with nucleophiles are presented mainly in reactions of chloro derivatives with an anionic nucleophile (alkoxide) and with a neutral nucleophile (ammonia or aliphatic amine). It is obviously beyond the scope of the present review to include the vast amount of work involving all nucleophilic displacements on azines and their different derivatives. However, we have attempted to include examples of all work which clearly demonstrates the relative reactivity of rings or of ring-positions. The term "nucleophilic substitution" is used in its proper general sense to mean the substitution, by any entering group, of hydrogen or any other leaving group.

B. ESTIMATES OF ELECTRON DISTRIBUTION AND REACTIVITY

1. *Theoretical Calculations*

Electron distribution and localization energies of azines have been the subject of extensive theoretical calculations employing valence-bond and molecular orbital methods whose applicability is still in "a somewhat confused and unsatisfactory state."¹⁰ The utility and limitations of the results in relation to nucleophilic substitution in aromatic azines have been summarized by Albert^{11a} and by Ridd [cf. Section IV, A, 1 and reference 634(b)]. Depending on the calculations, a greater electron deficiency has been found^{12, 13, 14} at either the 2- or the 4-position, and usually the 2-positions are indicated to be the more electron-deficient in mono- and bi-cyclic azines. Some recent calculations¹⁵ arrive at a substantially greater electron deficiency for the 4- than for the 2-positions. These calculations generally can be used to account for reactivity at different positions in the same ring only. Still continuing are efforts to develop a theory capable of evaluating relative reactivities of two positions in different ring systems.¹⁶

Longuet-Higgins¹⁷ and Barnes¹⁸ have calculated the "atom localization energies" required to develop a positive charge at different ring-positions of an azine and a negative charge on ring-nitrogen. In heterocycles, predictions of orientations based on electron deficiency in the ground state often have differed from those based on localization energies. The agreement of either with experimental orientation varies with the cationization of the heterocycle, according to Brown.^{16b, 19} Various refinements¹⁰ of molecular orbital theory, such as self-consistent field calculations^{20a} with configuration interaction, are being explored for azines,^{20b, 21a} and alternative concepts of transition states are being examined.^{16a}

In summary, theoretical calculations have not been a reliable guide to relative nucleophilic reactivity at different positions in the same azine or at comparable positions in different ring systems, but they may become so in the future.

2. *Experimental Evaluation of Ground-State Electron Deficiency*

Various physical measurements yield data from which one can estimate the electron density, which is pertinent to relative chemical reactivity at different positions of a ring or to comparison of different rings. However, in most cases the data pertain to the ground state of

the molecule rather than to a state activated for nucleophilic substitution and, consequently, only large differences in estimated electron density correlate with differences in reactivity. Recently, the relative electron deficiency of some heteroaromatic rings and ring-positions in the ground state has been studied by means of nuclear magnetic resonance spectroscopy. The chemical shift of the ring-hydrogens gives an indication of relative electron deficiency, but its use can be complicated by ring-current anisotropy and by remote spin-spin couplings. Proton magnetic resonance has been studied^{22a} in pyridine, quinoline, and isoquinoline. Similarly, pyridine and pyridine 1-oxide as well as some derivatives have been related^{23a} as to electron densities. By means of the chemical shifts of the hydrogen atoms in pyrimidine and 4- and 5-substituted pyrimidines, it has been shown that the electron deficiency at the 2-position is greater than at the 4- or 6-position regardless of the nature of the substituent.^{23b} The α -positions are clearly the most electron deficient in all these azines. Fluorine (^{19}F) chemical shifts have been investigated^{22b} in benzene derivatives for the same purpose and are also subject to the same complicating effects. Another approach^{24, 25} to the charge distribution in pyridine, pyrimidine, *s*-triazine, and quinoline has been by means of the nuclear quadrupole resonance of chloro (^{35}Cl) or bromo (^{81}Br) substituents, which also shows a greater electron deficiency at the 2- than at the 4-positions. Lauterbur²⁶ and Muller and Pritchard²⁷ have shown that increasing the electronegativity of carbon increases the size of the spin-spin coupling constants of ^{13}C and the attached hydrogen, and that the small satellite peaks due to the natural abundance of ^{13}C can be employed to compare variously substituted carbons. This method, in which ring-current anisotropy is less of a problem, was applied to pyrimidine and its derivatives. It was reported^{28a} to be a more reliable index of the charge density and orbital character (C—H) in the ring than chemical shifts. Again the electron deficiency at the 2-position was greater than at the 4-position. The electron deficiency, as calculated^{28b} from the chemical shifts of the ring-hydrogens, is very similar for the 4- and the 2-positions in the pyridinium ion and that for the 3-position is greater than for the 4-position in pyridine.

The relative electron-donating ability of rings can be estimated^{29, 30} by the change in the infrared stretching frequencies of attached amino, carbonyl, cyano, or methoxy groups, but the quantitative relation to chemical reactivity does not appear to be defined at

present. The π -electron density at ring-carbons has been related to the frequencies and intensities of the N—H stretching absorption of carboaromatic and heteroaromatic amines.^{31, 32}

All these methods demonstrate that the 2-positions of pyridine, pyrimidine, and other azines are the most electron deficient in the ground state. However, considerably greater chemical reactivity toward nucleophiles at the 4-position is often observed in syntheses and is supported by kinetic studies. Electron deficiency in the ground state is related to the ability to stabilize the pair of electrons donated by the nucleophile in the transition state. However, it is not so directly related that it can explain the relative reactivity at different ring-positions. Certain factors which appear to affect positional selectivity are discussed in Section II, B.

C. ALTERNATIVE MECHANISMS OF NUCLEOPHILIC SUBSTITUTION OF AROMATIC COMPOUNDS

It is quite reasonable to expect the bimolecular two-stage mechanism (S_NAr2) to predominate in most aromatic nucleophilic substitutions of activated substrates. However, only in rare instances is there adequate evidence to rule out the simultaneous occurrence or predominance of other mechanisms. The true significance of the alternative mechanisms in azines needs to be determined by trapping the intermediates or by applying modern separation and characterization methods to the identification of at least the major portion of the products, especially in kinetic studies.

1. *Heteroaryne Mechanism*

The scope of heteroaryne³³ or elimination-addition type of substitution in aromatic azines seems likely to be limited by its requirement for a relatively unactivated leaving group, for an adjacent ionizable substituent or hydrogen atom, and for a very strong base. However, reaction via the heteroaryne mechanism may occur more frequently than is presently appreciated. For example, it has been recently shown that in the reaction of 4-chloropyridine with lithium piperidide, at least a small amount of aryne substitution accompanies direct displacement.^{34, 35} The ratio of 4- to 3-substitution was 996:4 and, therefore, there was 0.8% *or more* pyridyne participation. Heteroarynes are undoubtedly subject to orientation and steric effects which frequently lead to the overwhelming predominance of

one product³⁶ from benzyne and naphthalynes. Thus, the actual participation of arynes in a substitution cannot be determined merely by the product ratio, especially if the percent yield of characterized product is not nearly quantitative. From 3-chloro- or 3-bromopyridine, the "customary" aryne product ratio of 52:48 (4- to 3-substitution) was found, but the more reactive 3-fluoro analog gave a 4:96 ratio (only ca. 8% via 3,4-pyridyne). No trace of compounds resulting from 2-substitution via 2,3-pyridyne was found among the products from these three 3-halopyridines. 2-Fluoropyridine gave only 2-substitution with no trace of the 3-derivative. Kauffmann and his co-workers^{37,38a} have also demonstrated aryne substitution of 3-chloro-, 3-bromo-, and 3-iodo-quinolines but no aryne product from the 3-fluoro analog was demonstrable by paper chromatography. A report³⁹ of 3,4-pyridazyn participation was shown⁴⁰ in these laboratories to be erroneous. Introduction of the new substituent occurred at the 5-position in the reaction of 4-chloro-1-methyl-2-phenylpyridazine-3,6-dione with amines or methoxide ion.^{38b}

Czuba has studied the amination (KNH_2 in liquid NH_3 , -33° , 4 hr.) of the three bromo-1,5-naphthyridines.^{41a} The 3-bromo derivative gave an 82% yield of the 3-amino and a 13% yield of the 4-amino compound; no 2-amino derivative (via 1,5-naphthyrid-2,3-yne) was detectable. The 4-bromo compound gave a 70% yield of the 3-amino and a 20% yield of the 4-amino derivative; the higher proportion of the latter indicates some $S_N\text{Ar}2$ substitution is occurring along with the predominant 1,5-naphthyrid-3,4-yne mechanism. The ratio of 3- to 4-substitution is higher than with 3,4-pyridine but considerably lower than the ratio of α - to β -substitution with α - and β -bromonaphthalenes in such reactions. 2-Bromo-1,5-naphthyridine yielded 77% of the 2-amino product with no 3-amino isomer but curiously gave 1% yield of 4-amino derivative.

Den Hertog and his co-workers^{41b} have found that amination of 2-chloro-, 2-bromo-, and 2-iodo-pyridine with H_2N^- yields only 2-aminopyridine. However, the less activated 3-halopyridines and 3-halo-2- or -4-ethoxypyridines are aminated in the 2- or 4-positions via 2,3- or 3,4-pyridyne intermediates depending on the location of the alkoxy group. A very interesting migration of bromine was also observed. They have now studied^{41c} all 10 isomeric bromoethoxypyridines which frequently aminate (KNH_2 , -33° , 10 min) via the heteroaryne mechanism. 4-Bromo-3-ethoxy-, 3-bromo-2-ethoxy-, and 3-bromo-6-ethoxy-pyridines gave a 90% yield of 5-amino, 97% of

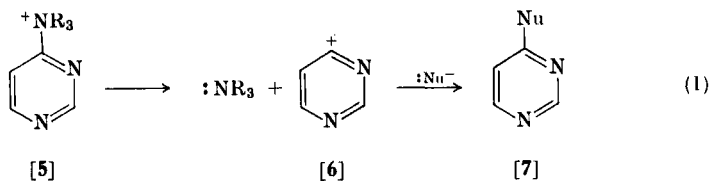
4-amino, and 65% of 4-amino derivatives of the corresponding ethoxypyridines. Curiously, 2-bromo-6-ethoxypyridine gave 10–15% yield of the 4-amino analog in addition to 80–85% yield of the 2-amino compound.

Since heteroarynes are thus seen to be subject to strong orientation effects, the detection of the occurrence of the aryne mechanism and the evaluation of the extent of its participation require a special approach. Both the aryne and S_NAr2 mechanisms can occur together, and variation of the leaving group on a substrate (e.g., 2-halonaphthalenes) can cause a complete shift³⁶ from the aryne (2-chloro, -bromo, and -iodo) to the S_NAr2 mechanism (2-fluoro); see also Section II, D, 1.

Studies of the reaction of 3-deuteropyridine and 3-picoline with sodamide has shown that this type of amination does not proceed through a pyridyne intermediate^{41d} as had been postulated recently.

2. S_N1 Mechanism

Only one type of aromatic substitution has been established to proceed through the S_N1 mechanism: the decomposition of diazonium ions in acidic polar media⁴² to give aromatic carbonium ions (yielding phenols) and N_2 , apparently a critical leaving group. The reaction can proceed since the latter is a very poor nucleophile despite its two lone-pairs (estimated⁴³ to have 79% *s*-orbital character). In aromatic S_N1 reactions, there is no steric decompression,⁴⁴ as there is in aliphatic S_N1 reactions, to compensate partly for the energy of heterolysis. In contrast to the effect⁴⁵ in the aromatic S_N1 reaction above, reactivity in aromatic nucleophilic substitution increases with greater electron-attracting character of the aromatic component and its substituents. For these reasons, the formation of an even more electron-deficient heterocyclic carbonium ion (6) and a reactive electron-rich nucleophile (the departed leaving group) in close proximity to each other seems to be unlikely with substrates such as 5. S_N1 and S_NAr2 mechanisms can occur side-by-side as in the reaction of 4-nitrobenzenediazonium ion in aqueous bromide solution.^{46a} Miller^{46b} has proposed that the formation of 1,3,4,5-tetrahydroxybenzene by the action of a weakly



basic reagent (water) on a deactivated (with respect to S_NAr2) substrate (3,4,5-trihydroxyanilinium chloride) can be explained reasonably only by the S_N1 mechanism.

The S_N1 mechanism [Eq. (1)] probably will occur less frequently in azines than in carboaromatics as a result of the greater electron-attracting nature of the rings and the greater number of electron-deficient positions.

3. *Ring-Opening and Recyclization*

Cyclo-isomerization via ring-opening and reclosing is encountered in the reaction of some heterocyclic derivatives with nucleophiles.⁴⁷ This multi-stage process can also give products which appear to result from normal (S_NAr2) substitution. For example, Shaw⁴⁸ has re-investigated an old observation that attempted conversion of 6-amino-2-chloropurine into the 2-hydroxy compound produces instead the 2-amino-6-hydroxy isomer. He has now found that the "normal" direct displacement product is simultaneously formed in small amounts, but not by the S_NAr2 mechanism. Instead it was shown to result from the sequence (1) nucleophilic attack at the 2-position, (2) ring-opening and loss of the leaving group, and (3) recyclization. How frequently this alternative mechanism occurs is not known. We plan to deal with ring-isomerizations of heterocycles fully in a succeeding volume. This type of ring-opening involves bimolecular nucleophilic attack adjacent to the activating ring-nitrogen, with one exception.⁴⁹

4. *Synchronous or One-Stage Bimolecular Mechanism*

The lack of a uniform order of relative reactivity of the halogens in reactions of certain nucleophiles with nitro- and polynitro-phenyl halides led Parker and Read⁵⁰ to propose a one-stage mechanism for *some* aromatic nucleophilic substitutions. An alternative explanation within the framework of the two-stage S_NAr2 mechanism had been proposed^{51, 52} earlier. A range of mechanisms has been considered in the past by Chapman,⁵³ who properly points out that only in a limited number of examples is the evidence for the two-stage mechanism compelling even though the balance of evidence favors it.

The synchronous bimolecular mechanism for aromatic nucleophilic substitution involves unfavorable geometry (bonds made and broken are both in the plane of the ring and backside attack is not possible) and unfavorable energetics (one high-energy step is required

rather than the two lower-energy steps of the S_NAr2 mechanism). In an aromatic system there is lacking a reasonable possibility^{54a} of forming the linear and opposite half-bonds to the nucleophile and to the leaving group by means of the two lobes of an unhybridized p -orbital, as is characteristic of aliphatic S_N2 reactions. Objections to other forms of the synchronous mechanism have been presented by Bunnett and Zahler.^{54a} Chapman and Russell-Hill⁵⁵ regard the intermediate complex "as providing a good guide to the nature of the transition state." However, the exact nature of the one-stage mechanism currently being considered by its proponents and its relation to the S_NAr2 mechanism do not seem adequately defined. It is not clear how the attacking reagent can form an "intermediate complex type" of transition state without affecting the π -electron system as envisaged in the two-stage mechanism.

5. Additive Mechanism of Nucleophilic Substitution at Multiple-Bonded Carbon

The two-stage mechanism appears to be quite generally involved⁵⁶ in nucleophilic substitution at acyclic unsaturated carbon as well as at carbocyclic and heterocyclic carbon (cf. Sections I,D,1 and II,A). In the case of carbonyl carbon, this intermediate-complex mechanism is supported by the form of base-catalysis^{57a} of aminolysis of esters and by the exchange of ^{18}O during hydrolysis^{58-61a} of esters, amides, acid chlorides, and anhydrides. The mechanism of various reactions of acid halides is discussed in the review by Parker (cf. p. 71 of ref. 50), and of esters in the review by Whalley.^{61b} A tetrahedral intermediate complex has been used to interpret the reactions of hydroxylamine with n -butylthiolacetate,^{61c} of various amino compounds with ethyl benzimidates,^{61d} and of dimethylaniline with tetracyanoethylene^{61e} as well as the *cis-trans* isomerization of olefins^{61f} and the hydrolysis of ethyl thionbenzoate.^{61g} Reaction at olefinic carbon via similar intermediates is supported by the stereochemistry of the reaction of chlorocrotonates with ethylmercaptide ion⁶² and of bromostyrenes with iodide⁶³ and of haloethylene sulfones⁶⁴ with various nucleophiles. The mechanism is also regarded^{65a} as applicable to substitutions at acetylenic carbon (chloroacetylenes and p -toluenethiolate ion). Arens^{65b} has proposed that this formation of acetylenic thioethers and analogous reactions of acetylenes proceeds via nucleophilic attack at the halogen rather than at the carbon atom, forming $\text{R}-\text{C}\equiv\text{C}^-$.

D. EVIDENCE FOR THE S_NAr2 MECHANISM AND ITS CHARACTERISTICS

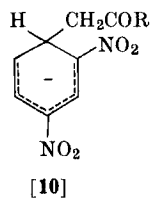
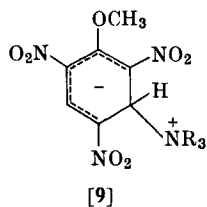
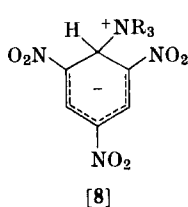
1. Evidence in Carboaromatics

The S_NAr2 mechanism^{54a} of aromatic nucleophilic substitution is theoretically sound and based on experimental evidence, the most decisive of which involves carbocyclic compounds. Strong support for the mechanism has been published by Bunnett and Randall,⁶⁶ in particular, the nature of the base-catalysis of the reaction of 2,4-dinitrofluorobenzene with *N*-methylaniline. The characteristic order ($F \gg Cl \cong Br \geq I$) of halogen reactivity⁶⁷⁻⁷⁰ in *activated* displacements and the lack of an "element effect"⁷¹ with different nucleophilic atoms has been put forth as evidence against partial bond-breaking being involved in the rate determination. The activation energy for displacement of halogen from 2-nitro-, 4-nitro-, and 2,4-dinitro-halobenzenes in ethanol with aliphatic amines or anilines is 4-5 kcal and with ethoxide 1-2 kcal lower for fluorine than for chlorine or bromine,^{72,73} in spite of the much higher bond energy of an aryl-F linkage. As a result of the decreased activation energy, the rate for displacement of fluorine in nitrohalobenzenes is about 1,000 times that for chlorine, bromine, and iodine in reactions with ethoxide or piperidine.⁷⁴ For other kinetic data on the relative reactivity of halogen groups see Section II,D,2,b and Tables VIII-XIII and XVI in Sections III,A,2 and IV,A,2.

The reverse sequence, $I > Br > Cl > F$, prevails^{75,76a} when carbon-halogen bond-breaking (second stage of S_NAr2) is rate-determining; e.g., in the reaction^{76a} of iodide ion with 2,4-dinitro-halobenzenes, the rate ratio is 120:1:0.06 for Br:Cl:F. Although this sequence is regarded⁵⁰ by some as evidence for a synchronous one-stage mechanism, Bunnett^{77a} has pointed out that failure to follow the "activated" order is not valid evidence for the synchronous mechanism nor for the aryne mechanism. Kinetic studies⁷⁸ of the reactions of a series of substituted phenoxide ions with 4-chloro-2-nitro- and 2,4-dinitro-chlorobenzene have been used to show (1) considerable bonding of the nucleophiles to the aromatic substrates in the transition states, and (2) the lack of significant alteration of transition-state structure upon drastic variation of reactivity.

Properties attributed^{79,80a} to the intermediate complex from reaction of 4-nitrofluorobenzene with azide ion were found^{80b} later to be due to an artifact resulting from photolytic decomposition of the

dimethylformamide solvent. Structures of the intermediate-complex type from polynitrobenzenes have been known^{54b,81} for many years and vary greatly in stability. Detailed studies on these "Meisenheimer complexes" have demonstrated⁸² that their formation from nucleophiles and 2,4,6-trinitrobenzenes is faster than formation of the displacement product. By low temperature spectrophotometry, Caldin and co-workers^{83,84} obtained evidence for the formation of such complexes as a sequel to the even more rapid formation of charge-transfer complexes from ethanolic ethoxide and 2,4,6-trinitroanisole, etc. They reported kinetic data for both processes. The methoxy products from 4-substituted 2,6-dinitrohalobenzenes not only are formed through such complexes but go on to form intermediate complexes⁸⁵ of their own with additional methoxide ion. 1,3-Dinitro- or 1,3,5-trinitro-benzene forms intermediate complexes^{86,87} such as **8** with ammonia and primary, secondary, or tertiary amines as nucleophiles. If a methoxy group is present, the reagents seem to attack at another carbon (cf. **9**). When such polynitro compounds are treated with alkali and a ketone,⁸⁸ the carbanion of the latter reacts to form an intermediate complex (**10**) which can react further to give the substitution product.



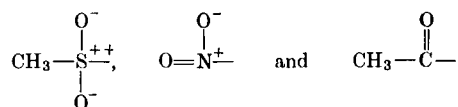
The nitro compounds above and 2,4-dinitrochlorobenzene form with aromatic, but not with aliphatic, amines^{87,89,90} "molecular compounds" which are probably charge-transfer complexes involving overlap of the π -electron systems. Formation of intermolecular charge-transfer complexes^{91,92a} or radical anions is an alternative interaction between electron-donor and -acceptor molecules or ions such as nucleophiles and aromatic substrates. Ross and Kuntz⁸⁹ demonstrated that nucleophilic substitution of 2,4-dinitrochlorobenzene with aniline is decelerated by formation of a charge-transfer complex. Deceleration can result if there is formed a large amount of such a complex having a lower free energy than the uncomplexed reagents (cf. Fig. 2, p. 168). The "sandwich" geometry in such charge-transfer

complexes will not be favorable for nucleophilic substitution and, in addition, the reactivity of the reagents will be lowered by this alternative way of satisfying their nucleophilicity and electrophilicity. Other similar complexes may have free energies and equilibrium concentrations such that the kinetic data are unaffected within experimental error. The significance of charge-transfer complexes as intermediates is still an open question. The azine nitrogen atoms in 2,4,6-tricyano-*s*-triazine confer greater charge-transfer complexing ability^{92b} than is present in the benzene analog as well as greater reactivity toward nucleophiles.

2. Characteristics of S_NAr2 Substitution in Carboaromatics

The factors in carboaromatic nucleophilic displacements summarized in this section are likely to be characteristic of heteroaromatic reactions and can be used to rationalize the behavior of azine derivatives. The effect of hydrogen bonding and of complexing with metal compounds in providing various degrees of electrophilic catalysis (cf. Section II, C) would be expected to be more extensive⁴⁷ in heteroaromatics.

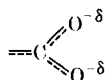
a. *The Effect of Charge in the Ground State.* The rate of nucleophilic substitution is increased or decreased by attraction or repulsion of the nucleophile by opposite or like charges on the substrate. Such Coulombic interaction varies with the inverse square of the distance and is still detectable for a substituent at the *meta*- and *para*-positions of a benzene ring. This effect of charge can produce an accelerative increase in the *entropy* of activation (see Section III, A, 2 and reference 482) in addition to resonance and inductive effects on the heat or *energy* of activation (see Section III, A, 2 and references 479, 481, 482). For example, in the reaction of 4-substituted 2-nitrochlorobenzenes with methoxide ion in methanol, the trimethylammonio group had the highest and least favorable activation energy of the polar groups but the highest and most favorable entropy of activation⁹³; the entropy of activation of substrates substituted with



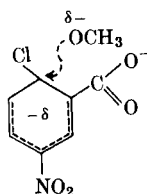
decreased with this decreasing order of dipolarity.^{93,94} In 4-substituted nitrobenzenes the 1:10:500 ratio of the reaction rates of

NO_2 , Me_3N^+ , and Me_2S^+ leaving groups is determined by the *entropy* of activation; the energies of activation of the first two are approximately the same while that of Me_2S^+ is substantially *higher*⁹⁵ and thus opposes the rate increase.

With methanolic methoxide and 4-substituted 2,6-dinitrochlorobenzenes, the substrate bearing a carboxylate anion as a substituent reacted more slowly than those with a 4-carboxamido or -carboalkoxy group. The rate difference^{70,85} between the anion and the latter groups is primarily an *entropy* of activation effect resulting from charge repulsion, the energies of activation of all three being similarly lowered with respect to that of the hydrogen in the 4-position. The counteracting, resonance effect



of the 4-carboxylate anion still makes it moderately activating for methoxy-dechlorination,^{85,96} relative to hydrogen. When a carboxylate anion is in the *ortho*-position, however, it is definitely deactivating^{77b,97a} due to a decrease in the activating resonance effect (see Section II, A) and to an increase in the electrostatic repulsion of attack by anionic methoxide in the transition state^{97b} shown in **11**.



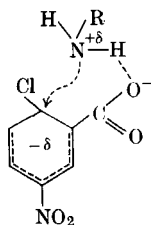
[11]

The importance of field effects of *ortho* substituents has been discussed by Miller and Williams.⁹⁶ The effect of various factors on reaction rates is depicted throughout mainly by means of transition states^{97b} rather than intermediate complexes whose properties are usually not rate-controlling.

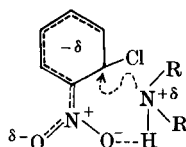
b. *Specific "Ortho Effects" and the Effect of Charge in the Transition State.* Although these interactions (see also Section I, D, 2, a) could also be considered as neighboring group effects or anchimeric assistance, they have been called "*ortho* effects" or "built-in solvation" by

workers in the field. In the transition state, acceleration will result from either hydrogen bonding by a substituent to an *extra* lone-pair of the nucleophile or hydrogen bonding by the nucleophile to a lone-pair of an appropriately located atom of a substituent.

Bunnett and co-workers^{97c, 97d} have shown that an *ortho*-carboxylate anion decreases the rate of reaction of 4-nitrochlorobenzene with methoxide ion but rather strongly increases the reaction rate with piperidine. This effect arises from an accelerative increase in the



[12]

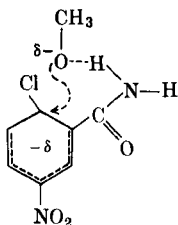


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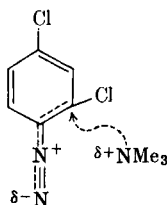
entropy of activation in the latter as a consequence of "built-in solvation." In *o*- and *p*-nitrochlorobenzenes, the *ortho* isomer reacts slower with methoxide ion but faster with piperidine,^{73, 97c, 97e} and the effect of change in solvent supports the "built-in solvation" explanation. In both these instances, hydrogen bonding (estimated^{97e} bond energy 2 kcal) and electrostatic attraction can act in concert to stabilize the *ortho* transition states^{97b} **12** and **13**. Ross and Finkelstein^{97f} have shown that the electrostatic effect *alone*, in the transition state from reaction with a tertiary amine, does not produce greater reactivity in the *ortho* isomer. The hydrogen bonding, proposed a decade ago by Chapman *et al.*,^{97e} is therefore the more significant factor. It will be stronger, of course, because of the apposition of the unlike charges. Comparative kinetic data for displacement of halogen from activated benzene derivatives with various nucleophiles (summarized by Reinheimer and his co-workers⁹⁸) shows that (*a*) activation energy is often greater for displacement by an anion (RO⁻) than by a neutral nucleophile (amines); (*b*) the entropy of activation is more negative (more rate-decreasing) for neutral than for anionic nucleophiles; and (*c*) the entropy of activation is considerably less negative and, therefore, more rate-increasing for reactions of primary and secondary amines with an *o*-nitro than with a *p*-nitro compound.

Electron repulsion (Section II, A) contributes to the effect described in *a*, but greater solvation of the anion is also important.

In methoxy-dechlorination of substituted nitrochlorobenzenes, the carboxamido group has a specific accelerative effect relative to acetyl, carboxylate ion, or carbomethoxy substituents,⁹⁹ presumably due to its hydrogen bonding to an *extra* lone-pair of the nucleophile, as in **14**, or to a lone-pair of the leaving group in other instances. Electrostatic repulsion in the *ortho* transition state **15** is a likely contributing factor to the selective reaction¹⁰⁰ of 2,4-dichloro- and 2,4,6-trichlorobenzenediazonium ion with trimethylamine at the 4-position, which is also favored by greater *para* than *ortho* resonance activation (cf. Section I, D, 2, c and II, B, 2) by the diazonium group.



[14]

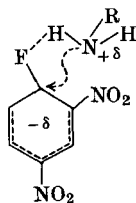


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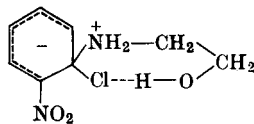
c. *Relative ortho, meta, and para Reactivity.* Applicability of conclusions on the *ortho* vs. *para* reactivity of carboaromatics to the behavior of heteroaromatics is limited by several complicating factors in carboaromatic compounds. Bunnett^{77c} attributes less effective conjugation to *ortho* activation, yet greater reactivity at the *ortho*-position is found for nitro or methylsulfonyl groups.^{101, 102} The relative *ortho:para* reactivity is a combination of steric and other interactions (see Section I, D, 2, b) and is sensitive to the nature of the solvent.¹⁰³ With nitrohalobenzenes, reactivity with anions (e.g., HO⁻ and CH₃O⁻) is greater at a *para*-halogen but with uncharged reagents (e.g., ammonia and amines) reactivity at an *ortho*-halogen is greater due to the hydrogen bonding in the transition state just discussed. A *meta*-activated group in nitrohalo- or nitromethoxybenzenes is clearly less reactive^{104, 105} than *ortho* or *para* groups towards alkoxide ion as well as other nucleophiles. However, activation is substantial: the reactivity of fluorobenzene (activation energy

36 kcal) is increased 100,000-fold by a 3-nitro substituent (decrease in activation energy of about 8 kcal). In nitrofluorobenzenes inductive *meta* activation is less than resonance activation by a rate factor⁷⁴ of approximately 10,000, and two *meta*-nitro groups are about as activating as one *ortho* or *para* group in terms of both rate and activation energy (decrease of about 15–16 kcal). 2,4-Dinitrofluorobenzene is only about 300 times as reactive as either mono analog; its decrease (24 kcal) in activation energy, relative to fluorobenzene, is only about 1.5 times as much as that in either mono-nitro compound. The effect of a second activating group is generally not decreased this much. It is interesting to note that, in the reactions^{73, 97c, 101, 103} of *o*- and *p*-nitrohalobenzenes with piperidine or methoxide, the activation energies for substitution at the *para*-position are 1–2 kcal lower; the rates give a variable relation. The lower activation energy for substitution *para* to an activating center seems to be a general rule (see Sections II, A, III, A, and IV, A for azine behavior).

d. *Hydrogen Bonding and Solvation*. Rate effects in the reactions of 2,4-dinitrofluorobenzene with amines have been attributed to high hydrogen bonding to the fluoro group in the transition state either by



[16]



[17]

excess amine⁷² or by the attacking nucleophile^{106a} itself (16). Acid catalysis via hydrogen bonding to the leaving group has been observed in benzyl fluorides^{106b} and alkyl fluorides.^{106c} Another example of the intervention of solvent in the decomposition of the intermediate complex is the acid-catalyzed hydrolysis¹⁰⁷ of 4-(*p*-sulfophenylazo)-1-naphthyl methyl ether where the slow step appears to be proton transfer from hydronium ion $[H_{2n+1}O_n]^+$ to the incipient methoxide ion. In the reaction of 2,4-dinitrochlorobenzene with *n*-butylamine in chloroform, accelerative hydrogen bonding of $n\text{-BuNH}_3^+$ to chloro in the substrate was noted.¹⁰⁸ Cyclic hydrogen bonding (17) to the leaving group has been proposed to explain the unique reactivity of ethanalamine.¹⁰⁹

The work of Miller and Parker^{80a, 80b, 110} on nucleophilic substitution of nitrohalobenzenes demonstrated that *lack* of solvation of the nucleophile by hydrogen bonding increased (as much as 50,000-fold) the rate of reaction, as a result of the decreased activation energy required. The rate increased with decreasing hydrogen-bonding capacity of the solvent (the effect of NH in liquid amides and of the CH in dimethylformamide being demonstrable). They also proposed that anionic intermediate complexes and transition states are more solvated in dipolar aprotic solvents than in protic solvents as are *large* polarizable inorganic and organic anions in general. This effect will reinforce the virtue of dipolar aprotic solvents in not deactivating nucleophiles by hydrogen bonding. Caldin¹¹¹ in discussing his own and earlier work considered that solvation changes en route to transition states make a considerable and sometimes predominant contribution to the energy of activation. He proposed that the lesser solvation of sulfur nucleophiles by hydrogen bonding is a very important factor in their greater reactivity compared to the more strongly hydrogen-bonded oxygen nucleophiles. It is clear that hydrogen bonding to a nucleophile's lone-pair (e.g., in ammonia) will decrease the reactivity of this lone-pair in nucleophilic substitution in proportion to the energy of hydrogen bonding (4–6 kcal \approx 50,000-fold rate decrease). Hydrogen-bonding solvation will decrease the reactivity of an adjoining lone-pair (e.g., in methoxide ion) as a result of the nucleophilic atom's decreased charge and basicity (toward carbon as well as hydrogen).

Salt effects on the reaction of 2,4-dinitrochlorobenzene with amines or alkoxides have been investigated.^{112a–114} Reinheimer *et al.*¹¹⁴ have studied decelerative ion pairing of alkali metal methoxides in reaction with this substrate; cations and anions in added salts have specific effects on ion pairing.

The effect of solvation of transition states has been discussed in relation to aromatic nucleophilic substitution.^{54c, 113, 115–117a}

e. *London Dispersion Forces.* The accelerative effect of London forces of attraction^{2b} between the nucleophile and a group *near* the site of attack at aromatic carbon has been proposed by Bunnett and his co-workers.^{51, 52, 117b}

f. *Effect of Leaving Group and Other Substituents.* The leaving group affects the reaction rate in several ways as discussed earlier in this section (I,D). The behavior of leaving groups in carbo- and hetero-aromatics is considered in relation to our main theme in Section II,D.

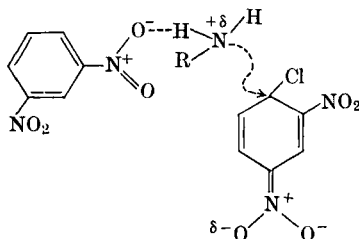
Investigations^{54d, 93, 94, 118} of substituted halobenzenes have demonstrated that (1) electron-attracting substituents accelerate nucleophilic substitution by lowering the activation energy (cf. Sections I, D, 2, a and I, D, 2, b) and (2) electron-donating groups decelerate nucleophilic substitution by raising the activation energy, both being more effective by resonance than by induction. An additional substituent sometimes produces a smaller quantitative, but similar qualitative, effect (see Section I, D, 2, c). The validity of the concepts of conjugation and hyperconjugation are being re-examined^{19a, b, 120-122}; the effects commonly attributed to them can be adequately explained in terms of hybridization^{119a, b} or of non-bonded interactions.¹²⁰

A nucleophile can interact reversibly with an electron-attracting substituent (e.g., $-\text{CN}$ or $-\text{CHO}$) in the course of nucleophilic displacement of another group (e.g., halo), thereby producing a spurious substituent effect (cf. 96). The interaction has been found to vary with the nucleophile⁹⁴ (see Section II, E).

The steric effects related to the coplanarity of an activating center^{77c, 97d, 101, 123} will not generally be applicable to azine activating centers. Other steric effects are directly applicable.

g. *Effect of Nucleophile.* Certain consequences of characteristics of the nucleophile are discussed above for carboaromatics and in Section II, F for azines. Variation of the nucleophile (Cl^- , HO^- , N_3^- , RNH_2 , RO^- , RS^- , etc.) produces large changes in the rate of reaction of a single aromatic substrate.^{54e, 77d, 124, 125a}

h. *Catalysis.* Catalytic effects of acids are noted in Section I, D, 2, d. From zwitterionic intermediate complexes (e.g., that formed from an amine and an activated aromatic substrate), proton removal by excess nucleophile or an added base sometimes facilitates nucleophilic substitution.^{66, 112b, 126, 127} In such cases, the measured rate is then a function of the constants for both the catalyzed and



[18]

uncatalyzed reaction and the concentration of the nucleophile or added base.¹²⁸

The catalytic effect of aromatic nitro groups in the substrate and product or in an *added* inert nitro compound (e.g., *m*-dinitrobenzene in **18**) has been observed¹²⁸ in the reaction of 2,4-dinitrochlorobenzene with an amine in chloroform. Hydrogen bonding to benzil or to dimethyl sulfone and sulfoxide also provided catalysis.¹²⁸ It is clear that the type of catalysis of proton transfer shown in structure **18** will be more effective when hydrogen bonding is to an azine-nitrogen.

II. Reactivity Factors in Azine Substitution by the S_NAr 2 Mechanism

The relative reactivity of azine rings and their ring-positions is determined by a number of factors that are considered in this section. Data and examples are taken up in Sections III and IV on the comparative reactivity of mono- and bi-cyclic azines. It is of interest to note that nucleophilic substitution comprises a sizeable section in the heterocyclic chemistry textbooks by Albert¹¹ and by Katritzky and Lagowski.¹²⁹

A. DETAILS OF S_NAr 2 SUBSTITUTION. AZINE INTERMEDIATE COMPLEXES

1. The S_NAr 2 Mechanism in Azines

The theoretical objections to the synchronous, one-stage bimolecular mechanism of aromatic nucleophilic substitution are reviewed in Section I,C,4. The two-stage mechanism is illustrated by the 4-substituted pyridine shown in Fig. 1. For steric reasons and to enable incipient bond formation, the nucleophile (Nu) will attack almost perpendicular to the plane of the ring, in the direction of the hybridized *p*-orbital of the reacting carbon. It encounters and is somewhat *repelled* by the π -electron cloud of the azine which in the ground state is polarized toward the nitrogen and is unevenly distributed (not shown) at the ring-carbons. The π -electrons will be perturbed by the encounter with the reacting lone-pair of the nucleophile, and, if the colliding components possess sufficient energy and their orbitals are properly oriented, the ring will proceed as far towards a localized stage (cf. **50** and Fig. 2) as the characteristics of the particular reaction require. The negative charge *always* donated by a nucleophile is stabilized in the transition state and in the intermediate complex (center of Fig. 1) by formation of a new resonating configuration where

the six π -electrons are now in a penta-atomic system. The molecule reverts to aromatic configuration upon departure of the leaving group (Le) with its bonding electrons.

As illustrated in the energy profile (Fig. 2), the substitution proceeds through the first transition state (T.S.¹) to the intermediate complex and then by way of a second transition state goes on to form the product. The transition state is the highest free-energy configuration

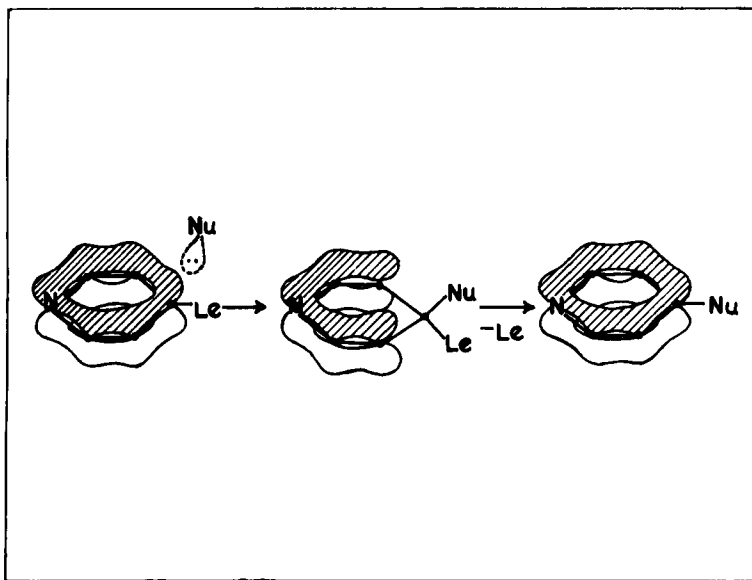


FIG. 1. Diagrammatic mechanism of nucleophilic substitution of an azine.

involved in proceeding to the product or to the intervening energy minimum. The free-energy change in reaching the transition state is the difference between the heat of activation¹³⁰ and an entropy of activation term (see Section III, A, 2). Frequently the heat or energy of activation determines the relationship of the reactivities. However, some rate differences and changes in positional reactivity are the result of entropy effects^{97c, 97d, 131} (cf. Sections I, D, 2, a and I, D, 2, b, and Table II in Section III, A, 2). The following factors contribute to the free energy of T.S.¹: (a) some fraction of the localization energy required to put a full positive charge on the reacting carbon and a negative charge in the resonating penta-atomic system (cf. 50), (b) forcing the leaving group into a tetrahedral position, (c) desolvating

the nucleophile, and (d) placing the nucleophile in a tetrahedral position with a lone-pair of electrons in the direction of the vacant orbital of the reacting carbon. This transition state then goes to the lower-energy intermediate complex by forming the Nu—C bond.

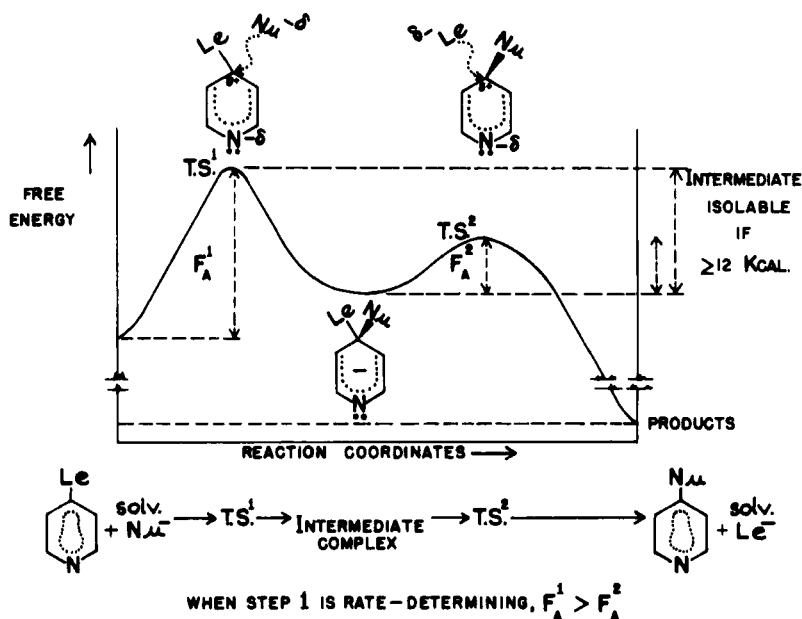


FIG. 2. Energy profile of S_NAr2 reactions.

Solvation changes of the heterocyclic substrate, transition state, and intermediate complex are also generally involved. Depending on the solvent, the transition state can be more solvated^{80a, 80b} than the reagents and, as a result, requires a smaller change in free energy. The second transition state is reached by rupture of the Le—C bond and, in forming the substitution product, regains the solvation energy of the leaving group and the ring localization energy defined above. Aromatic nucleophilic substitutions are kinetically controlled processes with the rate generally determined by a higher-energy first transition state.

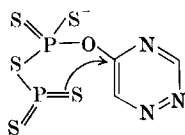
For unactivated aromatics, the activation energy (ca. 30 kcal⁷⁴) is less than the calculated localization energies (ca. 40 kcal for complete separation of charges in pyridine¹⁸), and, therefore, complete localization prior to reaching the transition state appears to be unnecessary

due to partial bond formation and solvation energy changes. With activated compounds, the energy of repulsion of the electron-rich nucleophile by the π -electron system (the energy required for it to accept electron donation by the nucleophile) will be lower when there is activation, resulting in a decrease in the energy of activation and an increase in the rate. The repulsion energy will be lowered by an electron-withdrawing substituent,¹³² by an sp^2 -hybridized azine-nitrogen (see Sections III, A and IV, A), or by an electron-attracting leaving group⁷³ (cf. Section II, D). Hammond¹³³ has suggested that the transition state of an unactivated aromatic substrate should be closer to the intermediate complex in the extent of tetrahedral bond formation than the transition state of an activated substrate. In the latter transition state (intermediate between sp^2 - and sp^3 -hybridization of the reacting ring-carbon), "long bonds" can form.

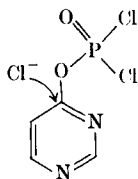
The greater the charge stabilization, the greater will be the depth of the energy minimum at the intermediate-complex stage, and the greater its stability. The intermediate complex from an unactivated substrate is unlikely to be detectable or isolable and even from activated molecules may not reach appreciable concentrations. The energy minimum may frequently not be occupied for an appreciable time.^{57b, 134, 135}

The S_NAr2 mechanism in reactions at heteroaromatic carbon atoms does not have the same kind of experimental support as it does in carbocyclic reactions. However, there appears to be no contrary evidence in these demonstrably bimolecular substitutions, and, therefore, we use it herein as the basis for interpreting azine reactivity.

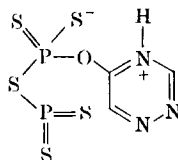
An intramolecular S_NAr2 mechanism (19) is possible in the replacement of oxo substituents with chloro or mercapto groups by means of phosphorus oxychloride or pentasulfide, respectively, via the intermediates shown. In the former, an intermolecular mechanism (20) is perhaps more likely. Frequently a base is not added in such reactions,



[19]



[20]



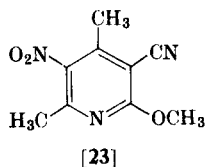
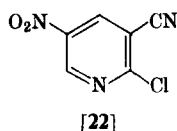
[21]

which are then acid-catalyzed via azinium structures such as **21** (cf. also **86**).

2. Evidence for Formation of Azine Intermediate Complexes

It should be pointed out that the existence of stable structures of the intermediate-complex type (also known as σ -complexes or Wheland complexes) is not of itself evidence for their being obligate intermediates in aromatic nucleophilic substitution. The lack of an "element effect" is suggested, but not established as in benzene derivatives (see Sections I, D, 2 and II, D). The *activated* order of halogen reactivity $F \gg Cl \cong Br \geq I$ has been observed in quantitative^{136a, 137} (cf. Tables II, VII–XIII) and in many qualitative studies (see Section II, D). The reverse sequence applies to some less-activated compounds such as 3-halopyridines,¹³⁸ but not in general.^{129a} Bimolecular kinetics has been established by Chapman¹³⁹ and others (Sections III, A and IV, A) for various reactions.

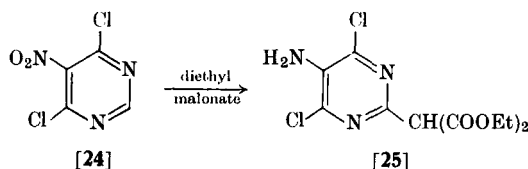
The relation of nucleophilic substitution in halopyridines to formation of a colored intermediate complex on the way to the product has been described by Mariella and co-workers.¹⁴⁰ Compound **22** and its 3,5-dinitro and 3-bromo-5-nitro analogs as well as its



6-methyl and 4,6-dimethyl derivatives react with alkoxide ion to give colors which are discharged when the product forms. When there are two substituents capable of resonance stabilization of the negative charge, the absorption maximum is shifted into the visible region of the spectrum. Colors were formed from hydroxide or alkoxide ion and less intense colors from acetate ion or ammonia. With the analogous, less reactive ether **23** the latter nucleophiles formed no color, but the former did. In the transamination of 2-alkylaminoquinolines with amide ion (H_2N^-), a colored intermediate was observed.¹⁴¹

Stable heterocyclic compounds having the intermediate-complex structure are well known. Where these compounds result from addition of a strongly nucleophilic anion to an *N*-alkylazinium cation or to a very activated substrate or must pass through a high-energy second

stage such as departure of H^- , they are easily isolable. Some require much more drastic conditions to carry out the second stage. The substitution of hydrogen may fail because of a lack of either sufficient activation or a suitable mechanism for removal of hydride ion. However, in suitably activated structures, the usually difficult substitution of hydrogen goes readily (via oxidation or autoxidation). In the reaction of **24** with diethyl malonate, the 2-hydrogen is substituted in preference to the usually reactive chlorine atoms, yielding the amine **25** via autoxidation. In activated polycyclic azines, oxidative nucleophilic replacement of hydrogen by amines, hydroxylamine, or thiophenols takes place rapidly at moderate temperatures. Thus, phenanthridine can be directly aminated by ammonia



(in air), and 5-nitro-, 7-nitro-, and 8-nitro-quinolines react with hydroxylamine to give 8-amino derivatives of the first two and the 5-amino derivative of the last.¹⁴² 8-Nitroquinoline on heating (in air) with a methanolic solution of thiophenoxide ion gives mainly 5-phenylmercapto-8-quinolylhydroxylamine with a small amount of 8-amino-5,7-bis(phenylmercapto)quinoline.

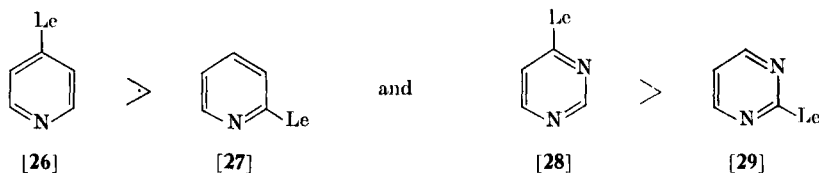
Heterocyclic structures analogous to the intermediate complex result from azinium derivatives and amines, hydroxide or alkoxides,¹⁴³ or Grignard reagents¹⁴⁴; from quinazoline¹⁴⁵ and organometallics, cyanide, bisulfite, etc.; from various heterocycles with amide ion,¹⁴⁶ metal hydrides,¹⁴⁷ or lithium alkyls¹⁴⁸; from *N*-acylazinium compounds and cyanide ion (Reissert compounds)¹⁴⁹; many other examples are known. Factors favorable to nucleophilic addition rather than substitution reactions have been discussed by Albert,^{11b, 150} who has studied examples of easy "covalent hydration"¹⁵¹ of heterocycles.

Careful study of mild conditions and of the effect of aprotic solvents will undoubtedly suggest methods for obtaining isolable intermediate complexes or lead to spectral evidence for their presence in many other reactions of azine derivatives with nucleophiles.

B. ACTIVATION BY AZINE-NITROGEN AND OTHER FACTORS IN THE NUCLEOPHILIC SUBSTITUTION OF AZINES

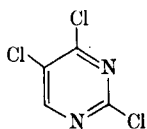
Recent studies, cited in Section I,B,2, demonstrated that the position *ortho* to a ring-nitrogen is more electron-deficient than the *para*-position. Certain factors associated with this ground-state electron deficiency are involved in the reactivity toward nucleophiles, and the more "electron-deficient rings" are the more reactive. However, in comparing the reactivity of different ring-positions, especially in the same heterocycle, subtle differences arise which affect the application of the "ring electron deficiency" to the lowering of the energy of activation of the various positional transition states. A limitation in most of the theoretical considerations of reactivity is the assumption of constancy of entropy of activation, which has been found to be subject to quite specific variations in benzene and azine derivatives (see Sections I, D, 2, II, E, III, A, and IV, A).

We present below an interpretation of azine substitutions based on the principle that reactivity is greatest *para* to the activating nitrogen (26–29) unless specific *ortho*-directing effects intervene. This principle applies also to the greater

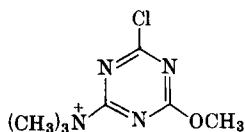


activating and deactivating effect of substituents from azine positions *para* to the leaving group. There are conflicting views in the heterocyclic literature on the applicability of the opposing concepts of (a) greater "inductive" activation at the more electron-deficient position *ortho* to the azine-nitrogen and (b) greater resonance activation at the *para*-position due to the lower energy of *para*-quinoid resonance structures. These concepts differ mainly in the relative importance assigned to ground state and transition state effects on the reactivity. It seems certain that the relative positional electron deficiency in the ground state of an azine is drastically perturbed by the approach to and interaction with a nucleophile. Since a reacting azine with alternative positions for reaction has a single ground state and only

one ground state energy, reaction will proceed most rapidly at the position where all marked resonance and inductive interactions produce the transition state requiring the smallest free-energy change. The reactivity at different positions is explicable by differences in electron-repulsion effects and in Coulombic interactions of several kinds in the transition states, as well as differences in localization energies. Relative positional reactivity always involves the ratio of reaction rates since the nucleophile reacts at all the possible positions regardless of the leaving group, e.g., in **30** and **31**. The very slow reactions at the positions with less activation or poorer leaving groups may be detectable only by special modern methods as used in the hetero-aryne studies^{34,35} referred to in Section I,C,1.



[30]



[31]

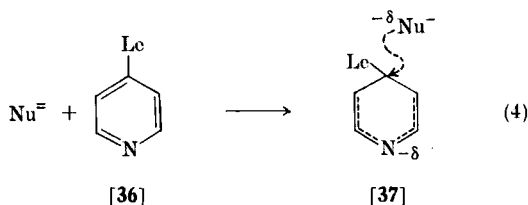
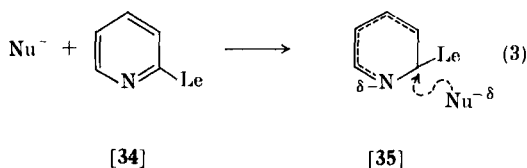
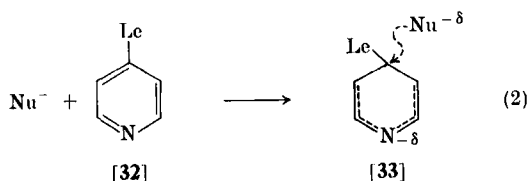
The specific effects which can increase reactivity at the *ortho*-position are (1) minimizing the separation of opposite charges in the transition state, (2) complete or partial cationization of the azine-nitrogen, (3) hydrogen bonding of the nucleophile to the azine-nitrogen, and (4) cyclic transition states involving the azine-nitrogen. The effect of cationization will vary with the charge on the nucleophile. In heterocyclic nucleophilic substitution involving these factors, the entropy of activation is less likely to be constant or to vary in a proportional, compensating fashion^{152a, 152b, 152c} with the energy of activation than in isocyclic reactions; rate relations primarily due to differences in the entropy of activation are thus more likely to occur. Comparison of the relative activation by the azine-nitrogen by means of activation energy rather than reaction rate has the advantage that the former is independent of the *specific* entropy of activation differences but has the disadvantage that it varies with the solvation energies of reagents and the transition state when the solvent is changed. Perhaps the basis of comparison should vary with the type of substrate and of reaction. Leffler^{152b} and Bunnett^{152c} have pointed out that, when the heat and entropy of activation increase or decrease proportionately, the reactivity relations are inverted above and

below the (isokinetic) temperature at which the rates are equal. Above this temperature, the rate relation is governed by the entropies of activation, and below it by the heats or energies of activation.

In compounds bearing several different groups there will be a complex interaction of activation by the azine-nitrogen with activation or deactivation by the substituents (Section II, E). The complexity of the interaction is emphasized by the realization that the effects of two identical substituents in an azine (e.g., in 2,4-dichloropyrimidine) are not the same on each other (Section II, B, 2, a).

1. Charge Types In Nucleophilic Substitution

a. *When the Nucleophile Is Anionic*, the transition state involves dispersal of the negative charge, and one factor in its free energy will be lowest when this charge is distributed over the atoms most widely separated in space (**33** vs. **35**). The benefit of charge dispersal should



be greater with a polyanionic nucleophile such as the sulfide ion (S^{2-}), in which case the nucleophilic atom retains at least a full negative charge (**37**). In such reactions of azines, this electrostatic

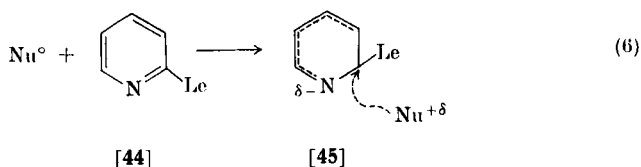
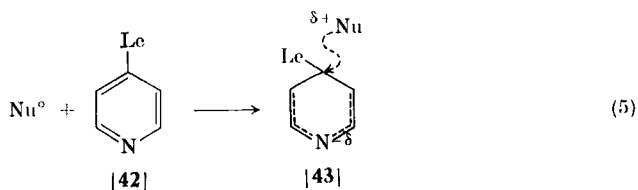
effect and the electron repulsion of the nucleophile by the high electron density of the ring-nitrogen combine in favoring reaction¹⁵³ opposite to, rather than adjacent to, the activating center. Increased reactivity in certain aliphatic S_N2 displacements has been explained^{154,155} as resulting from charge dispersal in transition states (with nucleophiles such as acetate, azide, and thiocyanate in which the charge can be distributed over several atoms). Charge dispersal over a greater volume in space may be significant in causing the reactivity of nitrochlorobenzenes towards ethoxide ion to be greater than that of the chloropyridine analogs.⁵⁵ This effect would be much greater in comparing the "ortho compounds" **39** and **41**. There is in fact

Approximate relative rates at 20°	400	80	40	1
	[38]	[39]	[40]	[41]

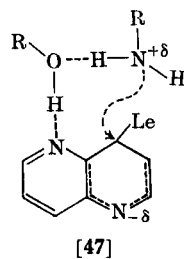
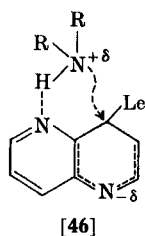
a larger difference between these analogs in spite of the fact that the reactivity of 2-chloropyridine is affected (see Section II,B,3) by hydrogen bonding of the solvent (in this case, the conjugate acid of the ethoxide ion) to the ring-nitrogen. The analogous hydrogen bonding to an oxygen atom of the nitro group is not appreciable in **39**.

In comparing resonance activation by nitrogen in the same ring with that by nitrogen in the adjoining ring of a bicyclic azine, other effects must be considered besides the volume over which the charge is distributed (Section IV, A).

b. *When the Nucleophilic Atom Is Not Negatively Charged* (NH_3 , R_2S , etc.), the transition state involves the incipient formation of a zwitterion and the associated factor in its free energy will be lowest when the separation of the two opposite charges is minimal (**45** vs. **43**). The electrostatic force between charges varies with the inverse square of the distance between them. This zwitterionic effect in transition states will still not determine the position of greatest reactivity unless it overcomes the difference in energies of charge stabilization at the ring-positions (cf. Section I, D, 2, b). Kinetic data (cf. Table VII in Section III, A, 2) for the reactions of 2-chloro- and



4-chloro-3-nitropyridines with pyridine as the nucleophile show that this electrostatic effect does not overcome the greater reactivity of the 4-position. When the nucleophilic atom bears a proton, its removal by a base and the formation of a second intermediate complex (now anionic) can slow the reverse reaction and facilitate the departure of the leaving group with the attached pair of electrons, e.g., base catalysis of the amination of trichloro-*s*-triazine (cf. Table VI in Section III, A, 2). It seems likely that amination of certain bicyclic azine derivatives will be accelerated by hydrogen bonding (46) or by facilitation of deprotonation (or charge neutralization) of the zwitterionic transition state; either effect may be solvent-assisted (47). Possibilities analogous to 46 and 47 exist for monocyclic azines also (Section III, A, 2).



In reactions at the sulfur atom of a sulfinate ion to form a sulfone, of a sulfoxide to form $\text{R}_3\text{S}^+-\text{O}^-$, or of bisulfite ion to form a sulfonic acid, the fractionally positive sulfur becomes more positively charged in the poly-ionic transition states. Definitive experimental evidence

is lacking on the relation of *ortho* vs. *para* reactivity determined by the net effect of the various possible electrostatic interactions in such transition states. The structure of the product obtained from the reactions of such sulfur-containing nucleophiles may be determined by (1) much stronger hydrogen-bonding solvation of the more negatively charged and smaller oxygen atoms or (2) rapid and reversible reaction at the more electron-rich oxygen atoms along with slower and less reversible reaction at the sulfur atom.

The accelerative effect of electrostatic attraction between anions and positively charged substrates and the decelerative repulsion of like charges in the reagents is discussed in Sections I, D, 2, a and b, II, B, 4, and III, A, 2.

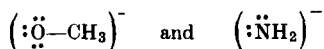
2. Orientation and Number of Ring-Nitrogens

There are conflicting generalizations in the heterocyclic literature as to the relative reactivity of α - and γ -positions in azines toward nucleophiles. Variations in the relative reactivity are attributed in this and subsequent sections to specific factors operating in addition to activation by azine-nitrogen. Another possible source of variation may be a decrease in selectivity with increasing reactivity of one or both reagents,^{135, 156-158} an effect established in electrophilic aromatic substitutions.¹⁵⁸

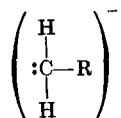
a. *Greater Reactivity at the Gamma than at the Alpha Position* is postulated to be the result of small differences in transition-state energy produced by several effects. Electron repulsion^{125a, 125b} between occupied lone-pair orbitals of the nucleophile and the π -electron system and the lone-pair orbital of the ring-nitrogen will be small in absolute magnitude since the geometry allows far less than maximal interaction. However, the magnitude may well be sufficient to affect the rate of reaction. Edwards and Pearson^{125a} discuss another aspect of this repulsion based on the Pauli exclusion principle and point out that it is far greater than simple electrostatic repulsion. Electron correlation in aromatic compounds has been reviewed by Dickens and Linnett^{159a} and its effect in reactions^{160, 161} and ground states¹⁶² has been considered. The π -electrons at an unsaturated atom provide a barrier against nucleophilic, but not against electrophilic, attack.¹⁶³⁻¹⁶⁵ Attraction of these electrons by a substituent reduces the barrier and facilitates attack.⁶⁸

In cases where comparable data are available, the activation energy for nucleophilic substitution by anions such as methoxide ion is

greater than that for neutral nucleophiles such as piperidine.⁹⁸ We expect the effect of electron repulsion to be greater for an anion with several lone-pairs such as

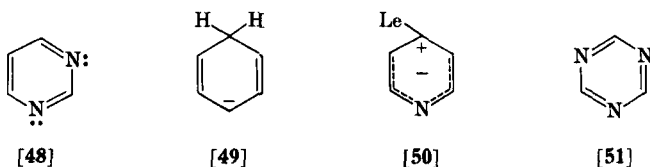


than for an anion such as



Small differences (ca. one kcal) in the energy of activation (10–30 kcal) may result from the difference in electron repulsion when reaction occurs next to the electron-rich nitrogen of pyridine as compared to reaction opposite to it. Where the localization energies for reaction at alternative α - and γ -positions are comparable, as in pyridine (ca. 40 kcal),¹⁸ the slightly greater repulsion adjacent to the centers of high electron density can tip the balance in favor of reaction at the position opposite to the ring-nitrogen.

In other heterocycles such as pyrimidine (**48**), the reactive positions are either between two centers of high electron density, the 2-position, or opposite one and adjacent to the other such center, the 4-position.



The electron repulsion between the nucleophile and the electron-rich ring-nitrogens is postulated to make the activation energy slightly lower for transition states where the electron-rich centers (nucleophile and ring-nitrogen) are farthest apart.

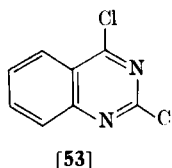
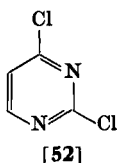
Another factor in determining comparative positional reactivity is the localization energy¹⁸ required to produce **50** or some form approaching **50** as the substrate reaches the transition state under the influence of the nucleophile. Experimental results on azines and theoretical considerations warrant the *general* postulate that the localization energy will be lower when a nitrogen atom is at the

center of the anionic resonating penta-dienoid system (cf. Fig. 2) of the transition state than when it is at the end of such a system.

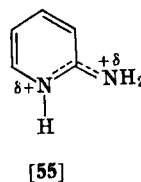
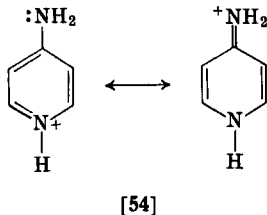
The resonating anionic penta-atomic system is similar in character to the anionic pentadiene intermediates in Birch reductions. Zimmerman¹⁶⁶ has interpreted the structural specificity (formation of 1,4-dihydro compounds by protonation of the central carbon of the anion) of Birch reductions as resulting from the greater charge localization at the center of the resonating ion (49) and has supported this view with molecular orbital calculations. In a penta-atomic system with a central nitrogen atom instead of a central carbon atom, charge localization at its center is reinforced, and the free energy required to reach the transition state is lower due to the decrease in the localization energy. Since the negative charge of the transition state can be distributed at atoms 1, 3, and 5 in the penta-atomic system, the location of the sp^2 -hybridized nitrogens at all three positions as in *s*-triazine (51) will produce maximal activation as a result of the most favorable resonance stabilization of the charge. Also, a 1,3 orientation of the nitrogens will produce a greater resonance stabilization and therefore greater activation than a 1,2 orientation. Further, the localization energy will be lower for substitution *gamma* or opposite to a ring-nitrogen than for substitution *alpha* or adjacent to it, since, in the latter case, nitrogen would tend to stabilize the charge at the end of the resonating pentadienoid anion. *Para*-quinoid structures are often considered^{136a,167,168} to be more stable than *ortho*-quinoid structures, and this idea is applied to transition states and intermediate complexes. In certain electrophilic reactions, the predominant *para* substitution is interpreted^{2c,e,169,170} as due to the lower energy required for *para*-quinoid charge stabilization. An additional stabilization of some transition states may result from their *symmetrical* resonance structure, e.g., 4-pyridyl, *s*-triazinyl, *s*-tetrazinyl, and 2-pyrimidinyl. The high basicity of *N,N',N''*-triphenyl- and trialkyl-guanidines relative to their mono- and di-substituted analogs¹⁷¹ is attributable to the completely symmetrical resonance in their cations.

In comparing the reactivity at different positions in a heterocycle, a poly-substituted derivative is sometimes used with the idea that selective reaction of the same leaving group at different positions in a single molecule gives the most clear-cut answer. However, in a polychloroazine, the mutual activation of the chlorines by one another is not identical (unless the molecule is symmetrical, in which case the

chlorines become identical). In 2,4-dichloro-pyrimidine (**52**) and -quinazoline (**53**), for example, the 2-chloro group will activate the 4-chloro group more than the reverse due to differences in their conjugative and inductive interactions with the rings.



Greater reactivity *gamma* to an azine-nitrogen would be expected on the basis of the greater *para*-quinoid than *ortho*-quinoid interactions between various substituents and azine-nitrogens in ground states and excited states. Such a difference in interaction is supported by several kinds of data: spectral,^{31, 172} basicity,^{129b, 173a, b, 174, 175} dipole moment,^{176, 177} and chlorine quadrupole resonance²⁵ of halo, methoxy, and amino derivatives of azines. The strikingly greater basicity of γ -aminoheterocycles (**54**) compared to the α -amino derivatives (**55**) involves conjugative and inductive effects similar to those discussed above, although in a thermodynamically controlled process.

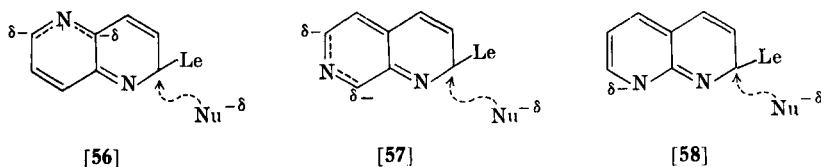


A proposed explanation of the reactivity of the 4-position versus that of the 2-position in pyridinium compounds has been advanced by Kosower and Klinedinst¹⁷⁸: “nucleophiles which are expected to form charge-transfer complexes will tend to substitute at the 4-position.” However, it is not clear why this (usually unknown) property should govern the site of substitution, except for a bifunctional nucleophile such as hydrosulfite ion which can form a suitable bridge from the nitrogen to the 4-position.

b. *Activation of a Meta- or Beta-Position by Ring-Nitrogen* is considered to result from inductive (electron-cloud deformation) rather than conjugative (electron transfer) interaction.

Inductive stabilization of charge in the resonating anionic pentadienoid system is produced when an electron-attracting sp^2 -nitrogen is next to one or more of the 1-, 3-, or 5-positions where the negative charge needs to be distributed in the transition state. Induction is considered by Taft *et al.*¹⁷⁹ to be a σ -bond effect and by Dewar and Grisdale¹⁸⁰ to be a field effect. "*Meta*" activation is strongest when the azine-nitrogen is in the ring being substituted since the inductive effect, whatever its nature, falls off with distance by an inverse factor.¹⁸⁰ The activation of 3-bromopyridine and of 5-bromopyrimidine is appreciable. Comparison of the reactivity of the latter with that of 2- and 4-bromopyridine could show whether the nitrobenzene relation (2 *meta*-nitro groups equal 1 *ortho*- or *para*-nitro group) discussed in Section I, D, 2, c holds true for azines.

When *nitrogen is in an "inductive position" of an adjoining ring*, the charge stabilization could be greater for a nitrogen atom at the *center* (5-position in **56**) of the pentadienoid transition state than at the 7-position (**57**), even though the distances from the reaction site are



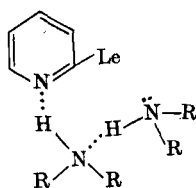
the same. However, this is not the case and the activation is the same on the basis of existing evidence (Section IV, A). If nitrogen is at a site (**58**) where the negative charge can be stabilized by resonance, it is more activating than inductive stabilization of the charge at two adjacent positions as in **56** and **57**.

3. Effect of Hydrogen Bonding to an Azine-Nitrogen

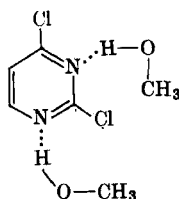
Hydrogen bonding to azines, a phenomenon well-established by spectral studies, is believed to be a neglected factor in relative positional reactivity. Hydrogen bonding to the ring-nitrogen lone-pair will produce partial cationization and a steric effect at the α -position. The steric effect would be accentuated if hydrogen bonding to the π -electrons as well as to the nitrogen lone-pair occurred in three dimensions (cf. Section II, C). The partial cationization presumably is a general activating influence (cf. Section II, C), not equal at the different ring-positions. It seems reasonable to postulate that transition states

in nucleophilic substitution of azines will always be strongly hydrogen-bonded in protic solvents at the ring-nitrogens which have therein become partly anionized.

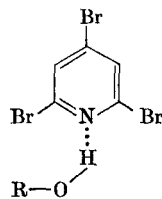
If there is hydrogen bonding to the azine by the solvent, three effects can result: (a) with an uncharged nucleophile such as an amine, steric hindrance to the reaction at the *alpha*-position, but not at the *gamma*-position, in a 4-substituted compound; (b) with an anionic



[59]



[60]

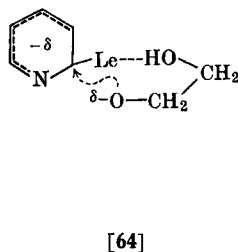
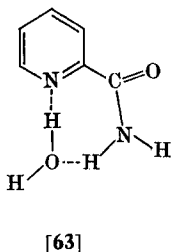
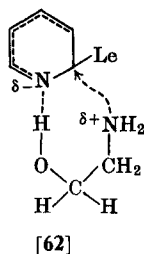


[61]

nucleophile (RO^- in ROH solvent), the steric hindrance at the *alpha*-position is counterbalanced to some extent by electrostatic attraction to the partly cationic center; and (c) with $\text{R}-\text{O}-\text{H}$ alone as reagent, the RO^- nucleophile is considered to be generated by the hydrogen bonding near the *alpha* reaction site. In the latter case, reaction nearest the ring-nitrogen would be favored relative to substitution by preformed RO^- . One example of this type of alteration of reactivity is the reaction of 2,4-dichloropyrimidine (**60**) with a methanolic solution of methoxide ions to give only 4-substitution, while methanol alone gives roughly equal amounts of 2- and 4-substitution.¹⁸¹ The resulting acid produces protonated **60** in equilibrium with the cation of the more basic product and autocatalysis may result. A steric effect of solvation would then operate in conjunction with a directive effect of protonation. Another example of altered reactivity is the extensive mono-substitution of **61** with phenoxide in water at the 4-position but with phenoxide in phenol at the 2-position¹⁸²; hydroxide in methanol gives a compound methoxylated at the 4-position.¹⁸³ Steric hindrance, which merely shields the reaction site, will decrease the rate by lowering the entropy of activation (and the Arrhenius frequency factor). However, if the group must be pushed aside to reach the reaction site, the energy so required will also decrease the rate by the consequent increase in the activation energy.

In aprotic solvents or in the liquid amine as solvent, the positional reactivity of amines is very likely to be altered, in the direction of greater *ortho* reactivity, by the hydrogen bonding of the amine reagent to the azine-nitrogen [involving one mole of each or a cyclic hydrogen-bonded structure (59)]. This effect is presumably responsible for some of the mixtures and changes in product ratio when the solvent is changed^{184a, 184b} (cf. Section III, B). Upon hydrogen bonding to the ring-nitrogen, the nitrogen or oxygen atoms in an amine or alcohol reagent become more negative and therefore more nucleophilic; in addition, the lone-pairs of these nucleophilic atoms are no longer randomly oriented with respect to reaction at the adjacent position.

A bifunctional reagent such as ethanolamine can favor *ortho* substitution of azines due to hydrogen bonding as in 62. With a bifunctional nucleophile such as ethylene glycol anion, facilitation of



substitution is possible via "solvating off" the leaving group as in 64 or hydrogen bonding to the azine-nitrogen or both.

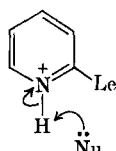
Hydrogen bonding to azine-nitrogen has been postulated to be responsible for 2-carboxamidopyridine being more rapidly hydrolyzed than the 4-isomer while the reverse is true in the esters.^{185, 186} Solvent-assisted indirect hydrogen bonding as in 63 is also possible.

4. Cationization and Protonation

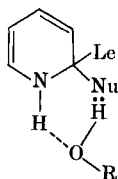
One significant difference between nitrocarboaromatics and aromatic azines is the tendency of the activating center of the latter to react with electrophiles or compounds capable of hydrogen bonding, thereby accelerating nucleophilic substitution.

Acid catalysis increases reactivity both *para* and *ortho* to the site of protonation. Coulombic attraction of an anionic nucleophile to the vicinity of the positive center will to some extent remove the proton (65), forming the less reactive azine and the nucleophile's

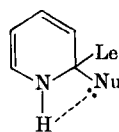
conjugate acid, and consequently lower the rate of reactivity at the *ortho*-position compared to the rate with irreversible cationization. If the nucleophile has two or more lone-pairs, its *extra* lone-pair in the *ortho* transition state and intermediate complex (67) can facilitate [via a hydrogen-bonded cyclic solvate (66), if necessary] proton transfer from the azinium center and thus reverse the reaction



[65]



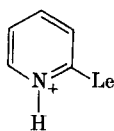
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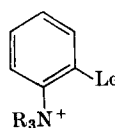
[67]

to some extent. Both of these processes of deprotonation tend to decrease the rate of *ortho* substitution relative to that at the *para* position in opposition to the effect of Coulombic attraction.

The accelerative effect of the protonated form (68) arises from increased resonance stabilization of the charge and is much greater than that which would result from its ammonio analog (69), activating by induction.

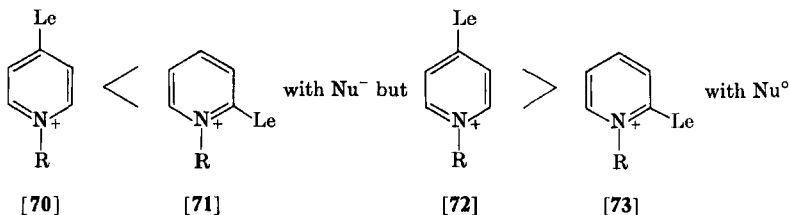


[68]



[69]

Irreversible cationization of the azine-nitrogen will increase the reactivity of anionic nucleophiles at the position adjacent to the azinium moiety (71 relative to 70), in the absence of substantial



steric hindrance by the ring-nitrogen substituent. This shift in relative reactivity presumably will not occur with uncharged or positively charged nucleophilic atoms, in which cases there would be electrostatic repulsion of like charges in the transition state, and **72** would exceed **73** in reactivity.

For further discussion of cationization effects see Sections II,C, III,A,2, and IV,A,2.

5. Cyclic Transition States

Greater reactivity with certain nucleophiles (metal hydrides, organometallics, acetylenic esters, etc.) adjacent to ring-nitrogen is postulated to be the result of simultaneous or prior electrophilic attack at nitrogen and the formation of a cyclic transition state. Nucleophiles like the methoxide ion react with a given substrate at the *para*-position while alkyl or aryl anions, Grignard reagents, and amide ions react at the *ortho*-position.^{187a} This difference may involve either the electron repulsion of the additional lone-pairs of the former, tending to decrease reactivity adjacent to the high electron density of the ring-nitrogen, or the intervention of a cyclic transition state in the case of these reagents can direct reaction adjacent to the ring-nitrogen. Eisch and Gilman^{187a} attribute the *ortho* substitution to the greater reactivity of these reagents causing the transition state to be shifted toward the ground state whose characteristics then have a greater effect on the free-energy change. Alternatively, greater reactivity is believed^{135,156-158} to lead to *lack* of selectivity. Since metal complexing of azine-nitrogen with these reagents occurs, it seems reasonable to explain their substitution reactions by cyclic transition states involving such complexing. In the reaction of the amide ion with the anion **74** at the 6-position, the considerable



electrostatic repulsion can be substantially overcome in a cyclic transition state such as **75**. Consistent with the postulation of electrophilic attack at ring-nitrogen and an associated cyclic transition state

is amination of quinoline at the 2-position with the more electrophilic barium amide, while potassium amide gives a mixture of 2- and 4-substitution products (Section IV, B, 2, a). Heteroarynes have been suggested as intermediates in such aminations but this proposal is in conflict with critical experimental evidence.^{41d} The more resonance-stabilized carbanions are less reactive and more selective, and thus react predominantly at the more activated *para*-position. The less stabilized carbanions should be correspondingly more reactive and less selective, but they are more ion-paired and more prone to form cyclic transition states such as **75** which favor substitution adjacent to the azine-nitrogen. Therefore, *greater* selectivity results. In the reaction of lithium alkyls and aryls with pyridines and quinolines, 2-substitution occurs without detectable (in some cases, even by vapor phase chromatography) 4-substitution.^{187b, 187c}

The importance of metal catalysis is suggested by the fact that exclusive 4-substitution of pyridine with alkylolithiums or alkylmagnesium halides occurs when free metal is present; exclusive 2-substitution otherwise occurs.^{187d}

Another factor in such substitutions is that the second stage, i.e., the departure of the leaving group (hydride ion), may generally be rate-controlling; the reactivity at different positions could then depend on the relative rate of electrophilic attack at hydrogen and its removal. However, recent work on the reaction of phenyllithium with pyridines and deuteropyridines shows that elimination of hydrogen is not important in determining the orientation of the product (no 4-substitution detectable).^{187c}

It is postulated that hydrogen-bonded cyclic transition states such as **62** or the analogous one involving $\text{HOCH}_2\text{CH}_2\text{O}^-$ will be found to increase relative reactivity adjacent to the azine-nitrogen in aprotic solvents; cf. also Sections II, E, 2, e and II, F.

6. Effect of Other Substituents on the Displacement of the Leaving Group

Steric hindrance to activation by carboaromatic nitro groups is well-known, but there seems to be no analogy in the chemistry of azines. The lone-pair of azine-nitrogen has a steric effect comparable¹⁸⁸⁻¹⁹⁰ to, somewhat greater^{191a} than, or somewhat less^{191b-191e} than a hydrogen atom. It is not certain whether bulky groups such as *t*-butyl produce a steric distortion of the lone-pair orbital and whether activation or deactivation results.

The principle of greater *para* activation (Section II, B, 2) applies

also to the activating (and deactivating) behavior of substituents, which exert greater effects from positions *para* to the leaving group (cf. Section II, E).

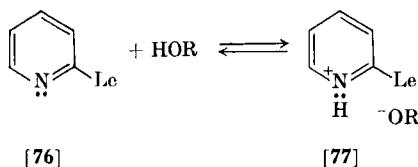
C. INFLUENCE OF CATIONIZATION OF THE AZINE MOIETY AND OF HYDROGEN BONDING TO THE AZINE-NITROGEN

Cationization of the azine-nitrogen promotes nucleophilic substitution at all positions since the electronegativity of the nitrogen is increased. This change increases the electron deficiency (ground state) and decreases the localization energy and resistance of the π -electron system to interact in the transition state with nucleophiles. The azinium moiety may result from alkylation, arylation, acylation, protonation, *N*-oxidation, metal complexing, or hydrogen bonding. Irreversibly cationized derivatives, for example *N*-alkyls, show an increase in reactivity which is not sensitive to reaction conditions as is the case for reversibly cationized derivatives such as the protonated form (cf. Section II, B, 4). In addition to the general activating effect (Sections III, A and IV, A), several other consequences are possible: (1) steric hindrance to *ortho* substitution due to the *N*-substituent or to the solvent hydrogen-bonded to an azinium NH; (2) electrostatic facilitation of reaction by anions and some deceleration of the reaction of non-anionic nucleophiles at the *ortho*-position; (3) interaction of the nucleophile with the *N*-substituent favoring *ortho* substitution (cyanide ion and *N*-acylazines¹⁴⁹). In general, the increase in reactivity at different ring-positions is not equal.

Although the reality of hydrogen bonding of azines with "inert" solvents and organic compounds has been established, its effect on their reactivity does not seem to have been considered. The effect on the alteration of the relative reactivity of different positions in the same ring is especially pertinent. The extent of interaction with a hydrogen-bonding or an electrophilic center will depend upon the electrophilicity of the latter and on the availability of the azine lone-pairs for sharing (less *s*-orbital character). Hydrogen bonding of the reagent or of the solvent to the oxygen atom of an azinone is discussed in Section II, E.

Hydrogen bonding with protic solvents or reagents occurs widely in azines even when they are not appreciably basic and the protic compounds are very poor acids. The latter do not have to be present

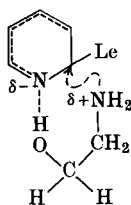
in large excess, e.g., as a solvent, for the hydrogen-bonded form to be predominant. The strength of such hydrogen bonds is substantial (4–5 kcal); qualitatively, the effect of hydrogen bonding is like that of protonation, and it may be quantitatively similar. Therefore, activation can be presumed to result from the partial cationization so produced, unless the nature of a particular transition state requires that hydrogen bonds be broken. In the latter instance, the activation energy will be increased by the heat of hydrogen-bonding solvation or the energy of desolvation and the rate will be decreased. Generally, the hydrogen-bonding ability of the ring-nitrogen will be increased in transition states and intermediate complexes relative to the ground states due to its increased negative charge and increased sp^3 character, in the order *meta* < *ortho* < *para* to the reaction site. Such hydrogen bonding will stabilize the transition states and intermediate complexes in this order. Definitive studies of the effect of hydrogen bonding on the nucleophilic reactivity of azines seem to be lacking, but some variations in positional selectivity can be rationalized on the basis of the steric effects of the hydrogen-bonding solvation of an azine-nitrogen. Where hydrogen bonding to the ring-nitrogen involves a hydrogen of the nucleophile or of its conjugate acid, reaction at the *ortho*-position can be accelerated relative to that at the *para*-position by a higher entropy of activation for the former. In an alkoxylation reaction [Eq. (7)], hydrogen bonding can lead to simultaneous generation (77) of protonated azine and an anion caged in by solvent in the vicinity of the adjacent reaction site (cf. Section II, B, 3).



Even without a “cage effect,” the entropy effect will be somewhat more favorable for *ortho* reaction when hydrogen bonding to an azine-nitrogen atom generates the necessary nucleophile. The possibility of proton transfers between the solvent molecules (MeOH) near the reaction site and the more distant MeO^- is expected⁹⁴ to produce a favorable increase (relative to other solvents) in the entropy of activation, which can reinforce the effect of a favorable point of

origin of methoxide ions. An alternative way to regard the proton-transfer possibility is that methanol molecules which are hydrogen bonded to MeO^- will be more nucleophilic than isolated solvent molecules since they can react by completing the proton transfer.

A hydrogen-bonded cyclic transition state can be postulated for a nucleophile like ethanolamine or ethylene glycol anion whose hydrogen bonding to an azine-nitrogen in aprotic solvents can facilitate reaction via a cyclic transition state such as **78**, cf. Section II, F. Ethanolamine is uniquely reactive¹⁰⁹ with 2-chloronitrobenzene by virtue of a cyclic solvate (**17**) of the leaving group, a postulate in line with kinetic evidence.



[78]

Various evidence for OH, OD, SH, CH, and NH bonding to azines has been summarized by Pimentel and McClellan.¹⁹² The change in the infrared stretching frequencies of water, alcohols, mercaptans, pyrrole, and chloroform produced by pyridine has been studied.^{192a} Hydrogen bonding of water or alcohols to a nitrogen lone-pair has been demonstrated by means of shifts in the electronic absorption spectra (lone-pair to antibonding π -orbital transition, $n \rightarrow \pi^*$) of pyridine, pyrazine, pyridazine, and *as*-triazine^{192b} and by means of fluorescence emission spectra of various polycyclic azines.^{192c} Infrared studies also give evidence^{192d} for hydrogen bonding of water, alcohols, phenols, amines, and pyrrole to π -electron systems like benzene.

Subsequent investigations have reinforced earlier evidence for the wide occurrence of hydrogen bonding of azines. Bonding of all the monocyclic azines,^{173c,d,193,194} many substituted azines,^{173e} and azinones^{173f} with water, alcohols, and dilute acids has been studied by electronic absorption spectra and the variation of the effect with changes in the position of the substituent noted. Quinolines and acridines with chloroform, alcohols, phenols, carboxylic acids, aniline, and pyrrole show the influence of hydrogen bonding on

fluorescence and phosphorescence.^{195,196} Raman spectra^{197,198} show the protonation or hydrogen bonding of pyridine and quinoline with aqueous acid, carboxylic acids, water, methanol, and phenol. Various physical methods were used to study hydrogen bonding of arylamines¹⁹⁹⁻²⁰¹ to quinoline and pyridine.

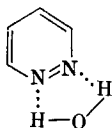
The association constant of pyridazine with ethanol was found to be 4.9 (from electronic absorption spectra) and 6.8 (infrared absorption spectra), and the corresponding values for the strength of the hydrogen bond are 4.2 and 4.6 kcal.^{202a} The hydrogen-bonded form of pyridazine was considered to comprise one alcohol at one azine-nitrogen at small mole ratios of alcohol to azine and to involve the second nitrogen at high mole ratios (an additional shift in the electronic spectrum. The association constants (3.1-3.8) of pyridine, quinoline, and isoquinoline with methanol in carbon tetrachloride have been determined by infrared spectroscopy.^{202b}

The catalytic effect of phenol, often interwoven with substitution proceeding through a reactive phenoxy intermediate, is not always pronounced.²⁰³ Phenols presumably have greater hydrogen-bonding and protonating capacity than alcohols, plus some attractive forces (charge-transfer complexing) between its electron-rich ring and the electron-deficient rings of the substrate.

Strong interaction of unsubstituted azines with water is indicated by their high solubility even when they are not appreciably basic (e.g., *s*-triazine, pyridazine, and *s*-tetrazine). Pyridine forms hydrates of definite composition²⁰⁴ and 1,5-naphthyridine strongly absorbs water and crystallizes as a hydrogen-bonded dihydrate.²⁰⁵ Solubility²⁰⁶ and thermodynamic studies²⁰⁷ plus the spectral work already mentioned demonstrate strong hydrogen bonding of water to mono- and bi-cyclic azines and indicate that *ortho* substituents can sterically affect hydrogen-bonding solvation.

The shift of the electronic $n \rightarrow \pi^*$ absorption²⁰⁸ of pyrimidine in water, relative to cyclohexane, is almost as great as that in 4*N* sulfuric acid. Pyridazine also shows similar shifts²⁰⁹ in water and acid, indicating a substantial amount of cationization in water. Azines exhibit a greater shift from the spectrum in hydrocarbon solvents when dissolved in water than in the more weakly hydrogen-bonding alcohols. The large spectral shift (corresponding to a heat of bond-formation of 10 kcal) of pyradazine in water has been ascribed²¹⁰ to a cyclic doubly hydrogen-bonded structure (79). An analogous seven-membered cyclic dihydrate seems more likely on steric grounds.

Hydrogen bonding to aromatic six π -electron systems is facilitated when it is intramolecular²¹³⁻²¹⁶ and is known^{217a} to occur with both O—H and C—H compounds. It is reasonable to assume that hydrogen bonding to an azine lone-pair will predominate over that to the azine π -electron system and that the latter will be further decreased by the former. More than one molecule of a compound capable of hydrogen bonding (e.g., an alcohol or an amine) is presumably involved to some extent in the hydrogen bonding to an azine lone-pair since the oxygen or nitrogen atom in the hydrogen-bonded alcohol or amine will be even more prone to form a hydrogen bond to another molecule of alcohol or amine than would an isolated molecule. The steric consequences (hindrance to *ortho* substitution) of hydrogen bonding to an azine-nitrogen and the likelihood of cyclic transition states (59) (facilitation of *ortho* substitution) would be thereby increased (cf. Section II, B, 5).

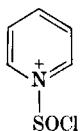


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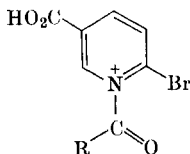
Quaternization or protonation of an azine-nitrogen will prevent hydrogen bonding to it and depress hydrogen bonding to other ring-nitrogens as well. Simultaneous hydrogen bonding to more than one azine-nitrogen in a ring seems to be possible (79) since the cationization is not complete, but bonding to the second nitrogen will be somewhat weaker. Diquaternization does not occur at all readily in an azine ring; e.g., only under special conditions (95%, but not 65%, H_2SO_4) is there evidence for even partial dicationization²⁰⁹ of pyrazine. Di-*N*-oxides are less stable than their mono analogs, even in pyrazine and quinoxaline where *para*-quinoid resonance can stabilize them. *Ortho*-quinoid resonance is generally weaker and, in a pyridazine di-*N*-oxide, would also have to overcome destabilization due to electrostatic repulsion of the adjacent partial positive charges on the nitrogens and of the negative charges on the neighboring oxygens. However, benzo[*c*]cinnoline 5,6-dioxides are known.^{217b} The effect of partial or complete cationization might be expected to be greater for a mono-azine than for a poly-azine in which the activation is greater. However, the effect in acid-catalyzed aminations was

found²¹⁸ to increase with the number of azine-nitrogens in spite of the decreased basicity.

Complexing with metal ions or acylation with organic or inorganic reagents produces reversible cationization of azines. The formation of metal ion complexes may facilitate reactions, as in the amination of 3-chloroisoquinoline in the presence of cupric ions,¹⁷⁵ or may be intimately associated with concurrent nucleophilic attack as in reactions of alkali amides,¹⁴⁶ metal hydrides,²¹⁹ or organometallics^{187b, 187c, 220} (see Section II, B, 5). Acylation with organic substances^{149, 221a} is more activating, but more susceptible to reversal, than alkylation. Acylation with inorganic compounds promotes nucleophilic substitution by activating the ring and often generates the nucleophilic reagent: 4-substitution of pyridine by means of thionyl chloride (cf. **80**)^{129c}; conversion of 2,4,6-trichloro-*s*-triazine into its fluoro analog²²² with SbF_3Cl_2 ; and preparation of bromopyrazines from the corresponding chloro compounds with phosphorous tribromide^{223a} and of chloropyridines from bromopyridines with thionyl or oxalyl chloride (cf. **81**).^{136a}

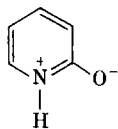


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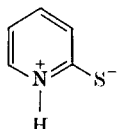


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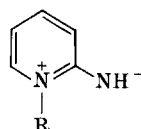
It is frequently not appreciated that the rings of azinones (**82**) and azinethiones (**83**) exist as partly cationized forms. These ring structures are resonance hybrids comprising a six π -electron aromatic system²²⁴ and are electron-attracting²²⁵ and activating in nature when they are zwitterionic, but not when they are anionic. One can expect that the cationic nature will be enhanced by hydrogen bonding (with solvent or with the nucleophile) to the anionoid atom, by protonation (e.g. of **84**), or by reaction with an electrophile [P_2S_5 thionations (**21**) and



[82]

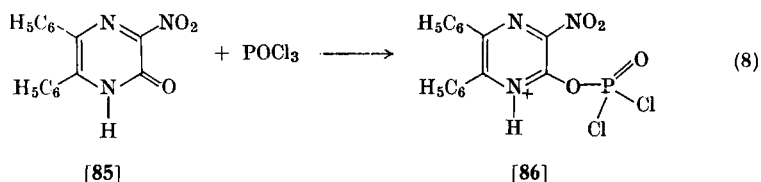


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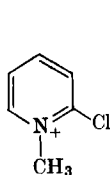
POCl_3 chlorinations (Eq. (8)) are acid-catalyzed reactions of such reaction products]. The hydrogen bonding of azinones is related to that of *N*-oxides, discussed below, and to that of ketones^{192f} (with water and alcohols) and has been demonstrated by infrared measurements on pyridinethione^{192e} in alcohols and by the electronic absorption spectra^{173b} of azinones in water. 6-Chloro-1,3-dimethylpyrimidine-2,4-dione is rapidly aminated at 20° (with heat evolution) by methyl- or ethyl-amines,²²⁶ etc., in protic media (water or alcohols). 5,6-Diphenyl-3-nitro-2-pyrazinone^{223b} (**85**) undergoes displacement of the nitro group (cf. Section II, D, 2, c) by halide ion in aqueous acid (protonation of the oxo oxygen atom), with thionyl chloride (formation of —O—SO—Cl which in this case does not go to chloro), and with phosphorus oxychloride [formation of —O—POCl_2 (**86**) which goes to chloro, but more slowly than nitro displacement occurs].



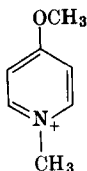
The azinones and their reaction characteristics are discussed in some detail in Section II, E. Because of their dual electrophilic-nucleophilic nature,²²⁷ the azinones may be bifunctional catalysts in their own formation (cf. discussion of autocatalysis below) or act as catalysts for the desired reaction from which they arise as by-products.⁴⁷ The uniquely effective catalysis of nucleophilic substitution of azines has been noted²¹⁸ for 2-pyridone.

Reactions of *N*-alkylated or arylated azinium compounds with nucleophiles proceed more readily than those of the parent, uncationized azines, and the ring tends to open.^{47, 221b, 228} The *N*-substituent may bring into play an accelerative effect from the London forces of attraction. Increased displaceability of the substituent in *N*-alkylazinium compounds has been noted for 2-halopyridinium^{229, 230} (**87**) 1-haloisoquinolinium,²³¹ 4-halopyrimidinium,²³² 4-methoxypyridinium²³³ (**88**), 4-phenoxy- and 4-acetamido-quinazolinium²³⁴ (**89**), 3-methylthiopyridazinium,²³⁵ and 2-carboxymethylthiopyrimidinium salts²³⁶ (**90**). The latter was prepared *in situ* from the *N*-alkylpyrimidine-2-thione. The activation can be effectively transmitted to

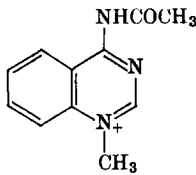
the adjoining ring, as in 3-chlorophenazonium quaternary salts^{129d} (**91** is reactive at 20° with aniline or acetate ion), and is sufficient to permit intramolecular nucleophilic attack by an alkoxybenzene double bond, as in 2-chloro-1- $[\beta$ -(3,4-dimethoxyphenyl)ethyl]pyridinium ion²³⁷ (cf. **247**). Heterocyclic pseudobases have been discussed by Beke.²³⁸



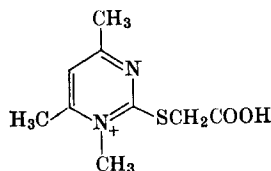
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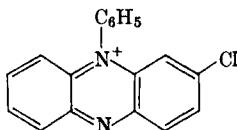
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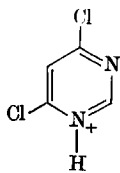


[91]

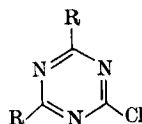
Kinetic studies on 2-, 3-, and 4-chloro-1-methylpyridinium salts showed a 30:10⁻⁶:1 ratio of the reaction rates at 50° with 4-nitrophenoxide ion in methanol.¹³¹ The activation energy for reaction at the 4-position is one kilocalorie lower (~ 8-fold higher rate) than for reaction at the 2-position. The reversal in rates relative to the corresponding halopyridines is the result of a much higher entropy of activation for the 2-chloro compound. The 3-chloro compound has a favorable entropy of activation also, but the energy of activation is about 13 kcal higher than that of the isomers (cf. Table II and Section III, A, 2).

The catalytic effect of protons has been noted on many occasions (cf. Section II, D, 2, c) and autocatalysis frequently occurs when the nucleophile is not a strong base. Acid catalysis of reactions with water, alcohols, mercaptans, amines, or halide ions has been observed for halogeno derivatives of pyridine,²³⁹⁻²⁴¹ pyrimidine^{242, 243} (**92**), *s*-triazine^{244, 245} (**93**), quinoline,^{203, 241} and phthalazine²⁴⁶ as well as for many other ring systems and leaving groups. An interesting displacement is that of a 4-oxo group in the reaction of quinolines with thiophenols,^{247, 248a} which is made possible by the acid catalysis.

An acid-catalyzed substitution of a 6-oxo group on 2-aminopteridine-4,6-dione with hydrogen chloride in alcohols (65–100°, 3 hr, 80% yield) represents a convenient synthesis of the 6-alkoxy analogs.^{248b} The reaction proceeds also with pteridine-2,4,6-trione and its 1-methyl and 1,3-dimethyl derivatives. While methoxylation of 2,4,7-trichloroquinoline gives about equal amounts of 2- and 4-substitution, acid-catalyzed hydrolysis gives specific reaction at the 2-position only.²⁴⁹



[92]

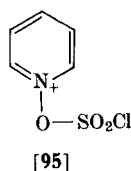
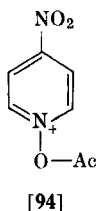


[93]

The kinetic data on the nucleophilic substitution of pyridine *N*-oxides and quinoline *N*-oxides, summarized in Sections III, A, 2 and IV, A, 2, show a strong activation which is greater than that produced by a nitro group. The activating effect of an *N*-oxide moiety will increase with hydrogen bonding of solvent or reagent molecules to its electron-rich oxygen atom. Ultraviolet,^{192b, 211} infrared,²¹² and Raman spectral data²¹² provide evidence for strong hydrogen bonding of alcohols, phenol, and water to the anionic oxygen of *N*-oxides. When the latter is bound to various electrophiles, it is possible to accomplish substitutions that do not take place with the parent azines, e.g., substitution of hydrogen with chloride ion in **95** (see also **249**). Activation of nitro- and halo-pyridines toward substitution with alkoxides, sulfite, or water by *N*-oxidation has been reported^{250, 251, 252a}; even the unreactive (toward sulfite, 185°, 16 hr) 3-chloropyridine was conveniently substituted in the form of its *N*-oxide (sulfite, 143°, 10 hr, 90% yield).^{252b}

The *N*-oxidation of 3-chloropyridazines increases their reactivity toward methoxide and sulfanilamide anions.^{253, 254} The reactivity of 4-chloro- or 4-nitro-quinoline and of chloropyridines toward methoxide ion and piperidine is less than that of the corresponding *N*-oxides^{137, 255a} (see Tables II and XI, pp. 270 and 338). The activating effect of the *N*-oxide moiety in 3-halopyridine *N*-oxides is greater than that of a nitro group, and in fluoroquinoline *N*-oxides the activation is transmitted to resonance-activated positions in the adjoining rings.^{255b}

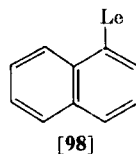
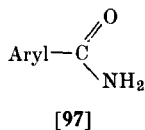
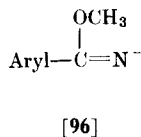
O-Acylation with acetyl chloride (giving **94**) or protonation permits rapid displacement of the nitro group from 4-nitropyridine *N*-oxide by the weakly nucleophilic chloride ion.^{256a, 256b} Pyridine *N*-oxide undergoes facile substitution of hydrogen by chloride ion (to yield 2- and 4-chloropyridine in 57:43 ratio) on reaction with sulfonyl chloride, presumably via the *O*-chlorosulfonyl derivative (**95**); 4-nitropyridine *N*-oxide yields 2,4-dichloropyridine.²⁵⁷



D. THE EFFECT OF THE LEAVING GROUP

1. General Effects and Summary

The leaving group is known to affect the rate of nucleophilic substitution of azines but there is very little information as to its effect on the relative reactivity of rings or of ring-positions. A decrease in positional selectivity in highly activated compounds bearing very good leaving groups might take place (see Section II, B, 2). In general, good leaving groups are also good activators of other groups for nucleophilic displacement, and poor leaving groups are deactivating. Groups that are anionized *under the reaction conditions* are poorly reactive when the atom attached to the ring is involved (e.g., —O^- , $\text{—N}^- \text{—SO}_2\text{R}$, etc.) but are more reactive when the charge is more distant (e.g., —SO_3^-). Some potential leaving groups undergo reduction in reactivity by readily adding the nucleophile reversibly to their own electron-deficient center (e.g., aryl-CN forming **96**); others proceed through irreversible decomposition of such an adduct to form a new and less reactive substituent (**97** from aryl-CN).



The leaving group (Le) can increase the rate of nucleophilic substitution through either a lower energy of activation or a higher (less negative) entropy of activation. Examples of both are known. The reaction mechanism itself can be altered to the benzyne or S_N1 type by the leaving group.³⁶ In the reaction of sodamide in boiling piperidine with **98**, the S_NAr2 mechanism occurs when Le is MeSO_2 , the benzyne mechanism when Le is Cl, Br, or I, and both occur when Le is F. Depending on the nucleophile, the fluoro and bromo derivatives react entirely by either one of the mechanisms.^{258, 259} The diazonium group in carboaromatics is the only leaving group known to undergo reaction (to give phenols) by the S_N1 mechanism (see Section I, C, 2). This behavior is not characteristic of other positively charged leaving groups and appears to result from the unique nature of the N_2 produced. Kloetzer^{260a, b} considered the S_N1 mechanism for the reaction of trimethylammonio heterocycles, but there is no experimental support for this possibility (see Section I, C, 2). Rate determination can be shifted to the second stage in reactions involving substitution of hydrogen (poor Le, H^-) or in halogen exchange reactions.^{76a}

The order of leaving group (Le) reactivity in heterocycles may be different from that in carbocycles on the basis of some reported reactivities which differ from the generalized mobility series of Bunnett and Zahler.^{261a} However, these authors and others have pointed out that "mobility" in carboaromatics varies with the nucleophile. The causes of the variation lead one to expect similar "irregularities" in heteroaromatics. Some of the variation observed with different nucleophiles, e.g., alkoxide vs. halide, involves a change in the rate-determining step, from the first to the second stage of the S_NAr2 mechanism.^{76a}

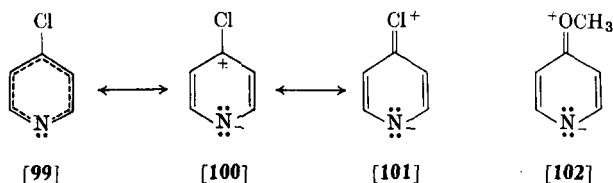
Reactivity increases with greater stability of the leaving group as an anion and with its lower basicity and lower nucleophilicity. These properties produce a low rate of reverse reaction of the product with the departed leaving group.

Other things being equal, one effect of lone-pair electrons in the leaving group would be to increase the energy of activation^{125b} by electron repulsion of the electron-rich nucleophile in the transition state and also in the intermediate complex. However, the net result involves electronegativity and size⁷⁰ as well. Compared with iodine, the more electronegative chlorine, with a shorter C—Le bond-length, is closer to the site of reaction and has a higher electron density but a smaller outer shell. Another effect of a strongly electron-attracting

leaving group is to increase, by induction, the electrophilicity of the reacting aromatic carbon in the transition state and to diminish the repulsion energy⁷³ in the formation of the transition state. The outstanding reactivity of fluoro, relative to other halogeno groups, in 2- or 4-halonitrobenzenes is ascribed⁷³ to this effect since solvation of transition states of the fluoro compounds is not accentuated. Halogeno groups in activated aromatics usually react with nucleophiles in the order $F \gg Cl \cong Br > I$, and some unactivated naphthyl halides also react in this order by the S_NAr2 mechanism.^{77a}

The different C—Le bond strengths arising from the reacting carbon being bound to different elements have a rather small effect on the rate of nucleophilic substitution of substituted benzenes.⁷¹

There is a difference of opinion about the *net* effect of resonance between the leaving group and an electron-attracting heterocycle, carbocycle, or substituent. This conjugation (101, 102) has been regarded^{169b,c, 262a, 262b} as a deactivating influence on nucleophilic substitution since the C—Le bond is lower in polarity and higher in

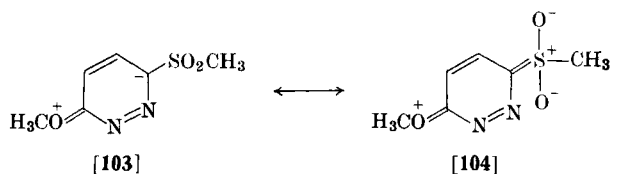


bond strength (more double-bond character) and the carbon has become less positive. The lower reactivity of chlorobenzene compared to alkyl chlorides is sometimes attributed to this resonance effect without considering the difference in mechanism and the energy of repulsion of the nucleophile by the π -electron system. All the more reactive aryl derivatives of such leaving groups (Le) involve *more* of such resonance than do the less reactive derivatives and this is true of aliphatic compounds also (cf. $RCOCl$ vs. RCH_2Cl or $R(C:CH_2)Cl$, $RCOOCH_3$ vs. RCH_2OCH_3 or $R(C:CH_2)OCH_3$). Such conjugation lowers the ground state energy and would thereby decrease the reaction rate if the free energy of the transition state either remains the same or increases, but both of these possibilities are very unlikely. The molecule is polarized in the direction of the transition state and the overall electron deficiency in the area of substitution may be increased

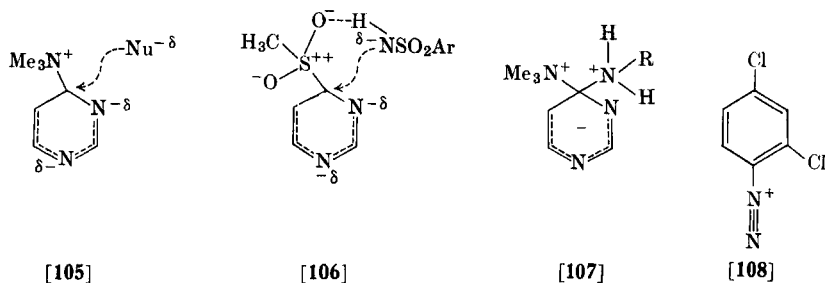
by conjugation. As a result one can reasonably expect (1) a compensating decrease in the energy of repulsion of the nucleophile by the π -electrons and by the lone-pairs of the conjugating group and (2) a compensating, favorable change in the entropy of activation due to this polarization. Reaction of a resonance hybrid, to which form **101** contributes, does not require rupture of, but only addition to, the $C=Cl^+$ bond and consequent complete restoration of the electrons to the electronegative Cl atom. Obviously we are not likely to get an exact determination of the effect of this resonance alone since it would require comparison of the reactivity of the same molecule with and without the resonance contribution. If one compares different leaving groups on the same ring or compares different rings bearing the same leaving group, the reaction rates would certainly be affected by the change in Le or in the ring and, therefore, the effect of concomitant changes in resonance of the types of **101** and **102** would not be clear. Some relatively unreactive, electron-donating substituents (e.g., methoxy and amino), when sufficiently activated by the presence of additional electron-attracting ring-nitrogens (e.g., as in 2-methoxy-*s*-triazine or 4-aminoquinazoline) or groups (e.g., methyl picrate), become quite reactive in structures which can hardly involve *less* conjugation with the electron-attracting centers. Bunnett^{54e} has expressed doubt that "double-bondedness" to the displaceable group is unfavorable to its replacement. He also pointed out that *p*-fluoronitrobenzene probably has the greatest $C-Le$ double-bond character and, yet, is the most susceptible of these halides to nucleophilic substitution⁶⁷⁻⁷⁰. The 2-pyridyl isomers of **101** and **102** are less conjugated but are also less reactive; the 4-pyrimidinyl analogs are more conjugated and more reactive; and the *s*-triazine analog is the most conjugated of all and also the most reactive. This general correlation of greater conjugation with the *greater* reactivity in compounds carrying leaving groups is not a valid basis for drawing a conclusion. The compensating factors in S_NAr2 substitution mentioned leave the net effect in doubt. In any case, it is misleading to consider only the deactivating aspect of this type of resonance in such compounds.

An interesting example of the result of conjugation of substituents is the behavior of 3-methoxy-6-methylsulfonylpyridazine studied in our Laboratories.²⁵⁴ In 6-chloro-3-methoxypyridazine and in 3,6-dimethoxypyridazine, the methoxy groups are unreactive toward sulfanilamide anion, and the chloro group is deactivated relative to

that in the 3-methyl, 3-chloro, or 3-unsubstituted analogs. The usually highly reactive^{263a, 264} methylsulfonyl group is very drastically deactivated, toward sulfanilamide anion, in 3-methoxy-6-methylsulfonylpyridazine by conjugation of the type shown in structures **103** and **104**. Simultaneously, the conjugated pyridazine methoxy group is activated so strongly that 95% of the product is formed by its displacement.

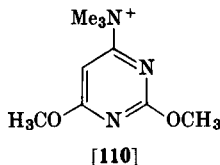
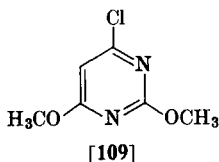


The high reactivity of leaving groups attached to heterocycles by a positively charged atom (e.g., SO_3H , SO_3^- , SO_2R , NO_2 , $^+\text{NMe}_3$, $^+\text{SMe}_2$) appears to involve an electrostatic effect on the entropy of activation which is more significant than that on the energy of activation (increased electrophilicity of the reacting carbon in the transition state). On pyrimidines, the 4-trimethylammonio and 4-methylsulfonyl groups are much more reactive than a 4-chloro group toward certain anionic nucleophiles, postulated^{263a} as electrostatic (e.g., **105**) and hydrogen-bonding (e.g., **106**) effects on the entropy of activation. Their relative reactivities at different positions of the same heterocycle seem to be unknown. It is reasonable to expect a favorable combination of entropy and energy of activation changes with anionic nucleophiles and a less favorable combination with uncharged or positively charged nucleophilic atoms. In the reaction of an amine with $\text{Ar}-\text{NMe}_3^+$, two positively charged groups become attached to the reaction site (cf. **107**), leading to a decrease in reactivity (unfavorable energy and entropy effect) relative to chlorine



(Ar-Cl), as compared to their reactivities with an anionic nucleophile. The reaction of **108** with trimethylamine at the *para*-position¹⁰⁰ contrasts with that of 2,4-dichloronitrobenzene which reacts with a large variety of nucleophiles at the *ortho*-position.^{97c} Compared to the (2,6-dinitrophenyl)trimethylammonium ion, steric hindrance to activating resonance would be much less in 2-trimethylammoniopyrimidine.

Hydrogen bonding of the leaving group with solvent or reagent in the ground state, transition state, and intermediate complex will make it somewhat more electron-attracting. This effect may be detectable by an increased rate of reaction if there is appreciably more solvation in the transition state than in the ground state or by a decreased rate if the solvation causes steric hindrance; or, the opposing effects may cancel. Fluorine, in the transition state and intermediate complex, would be more "aliphatic" and less conjugated via $C=F^+$ and therefore more readily hydrogen-bonded than in the ground state. Differences in the hydrogen bonding in a series of leaving groups may alter the order of their reactivity on changing the solvent.

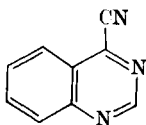


It is often advantageous to proceed to a desired product through two nucleophilic displacements rather than directly when one can exploit a difference in the reactivity of two leaving groups. An example^{263b} is the conversion of 4-chloro-2,6-dimethoxypyrimidine (**109**) (not satisfactorily reactive with sulfanilamide anion) by means of trimethylamine into the more reactive trimethylammonio derivative **110**. Conversion of chloro-quinolines^{36, 203} and -pyrimidines^{21c, 265a} into nitriles is best accomplished by conversion (with sulfite) into the sulfonic acids before reaction with cyanide.

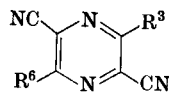
2. Leaving Groups

These are arranged alphabetically according to the atom attached to the ring: carbon, halogen, nitrogen (amino, nitro, etc.), oxygen (alkoxy, aryloxy, hydroxy, phosphoryloxy, sulfonyloxy, etc.), and

sulfur (sulfamyl, sulfonate, sulfonyl, thio). To facilitate comparison of the effects of leaving groups and of other substituents, the subdivision and arrangement of this section and of Section II, E, 2 are the same.



[111]



[112]

a. *Carbon*. In sufficiently activated azines, *acyl* groups are displaced. The reaction of metalloorganic compounds with *alkyl*- or *aryl*-azines can result in displacement of these poor leaving groups. The 4-alkyl group in α -(4-quinazolinyl)- α -phenyl- γ -diethylaminobutyronitrile was hydrolyzed^{262c} in boiling 50% sulfuric acid.

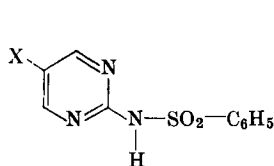
Many groups such as *carboxamido*, *carboalkoxy*, *amidino*, etc. are rather readily decomposed by nucleophiles. Some, such as *nitrile* and *aldehyde* groups, add nucleophiles reversibly (cf. 96).

Cyano groups can be highly reactive. 4-Cyanoquinazoline (111) is substituted by Grignard reagents without undergoing appreciable addition to the nitrile, which is also activated by the azine for nucleophilic addition. It is also very reactive^{265b, 266a, c} toward (acidic or alkaline) water, ketone carbanions, active methylene carbanions, phenoxide or alkoxide anions, hydrazine or aliphatic and aromatic amines. Displacement by alkoxide ions has also been investigated in pyrimidines.^{21b} Use of this group has not been extensive since it is often not as conveniently obtained as others. 2-Cyano- and 2,5-dicyano-3,6-dialkyl(or -diaryl)-pyrazines (112), available from direct synthesis, have been subjected to nucleophilic substitution²⁶⁷ by aqueous hydroxide (20°, 4 hr) and ethanolic ethoxide (20°, 10 hr) which displace only one cyano group. Tricyano-*s*-triazine is very reactive (Section III, B, 4, c).

Trihalomethyl groups have σ -constants^{268a} similar to those of the halogens but seem to be generally much less reactive than chlorine. However, convenient displacement of the former is often possible. Chlorine is more reactive than the trifluoromethyl group in 4-chloro- and 4,6-dichloro-2-trifluoromethylpyrimidine and the 5-nitro derivative of the latter; thus ammonia or hydrosulfide ion gave the 4- and 4,6-analogs. In the isomeric 2,6-dichloro-5-nitro-4-trifluoro-

methylpyrimidine, both chlorines are replaced by hydrosulfide ion (nitro also reduced); similarly, in the 5-amino analog, mono substitution gives the 6-derivative with ammonia or hydrosulfide.²⁶⁹

The trichloromethyl group in *s*-triazines is sufficiently reactive to be displaced by ammonia, amines, or alkoxides even if two deactivating groups have already been introduced.²⁷⁰ In contrast, under much more vigorous conditions benzotrichloride and 2,6-bis(trichloromethyl)pyridine are unreactive towards ammonia in dimethylformamide (2 hr, 165°).²⁷⁰ Tris-amination of 2,4,6-tris-(trichloromethyl)-*s*-triazine is complete in aprotic, but not in protic, solvents. 2-Chloro-4,6-bis(trichloromethyl)-*s*-triazine (**115**) reacts with primary and secondary alkanols to displace only chlorine.²⁷⁰ Although stable to these acid-catalysis conditions, the trichloromethyl groups can be replaced stepwise, after chlorine, with sufficient alkoxide ion. With one mole of nucleophile, the chlorine was replaced²⁷⁰ by arylsulfonylhydrazides, hydrazine, heterocyclic amines, hydroxylamine, thiocyanate, or triethylphosphite. Chlorine is also more reactive than pentafluoroethyl and heptafluoropropyl groups²⁷¹ on *s*-triazines. α,α -Dihaloalkyls have been little investigated.

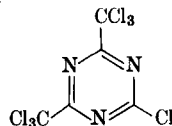


(X = halogen)

[113]



[114]



[115]

b. *Halogen*. The customary order of halogen reactivity in aromatic halides, especially when activated, is $F \gg Cl \cong Br \geq I$ (see Section I, D, 1, and for kinetic data on haloazines see Tables II, VIII–XIII) although the relative order for chloro, bromo, and iodo compounds varies with the nucleophile^{50,75,261b} and the solvent.⁷⁵ The values for the reaction of 4-nitrohalobenzenes with methoxide ion²⁷² in methanol (approximate relative rates at 82°, 400:2:2:1) and ethoxide ion⁶⁸ in ethanol (approximate relative rates at 91°, 500:2:2:0.2) show less of a spread than do the aliphatic S_N2 rates. The entropies of activation are all very similar and the rates reflect differences in activation energy (for fluorine it is ca. 4 kcal and for chlorine it is

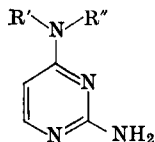
ca. 1 kcal less than for iodine). Similar results were obtained for the 2-nitro and 2,4-dinitro analogs, and there was less activation by a 3-nitro group.²⁷² In such reactions, bond breaking is not involved in the rate-determining transition state, and the electronegativity increases the electron-seeking nature of the attached carbon in the transition state. When the nucleophile is a halide ion, the series^{75, 76a-d} is reversed due to the importance of the relative ease of bond breaking in determining the rate (cf. Section I, D, 1). Comparatively little work has been done to establish the relative order in heterocycles and the effect, if any, on the relative positional reactivity.

There is some indication in pyridines and pyrimidines (113) that, when activation is by a "meta" azine-nitrogen, iodine and bromine are more reactive than chlorine.^{138, 273} In 2-halo-pyridines and -3-picolines^{136a} and -quinolines,²⁷⁴ fluorine is more reactive to acid hydrolysis than is chlorine or bromine, which are about the same. Halogen exchange under acid catalysis can be carried in a desired direction by mass action. 4,6-Dichloropyrimidine readily forms the diiodide from sodium iodide if acidified,²⁶⁴ although neutral sodium iodide at a lower temperature can be used²⁷⁵ with the more reactive tetrachloropyrimidine. Fluorine on *s*-triazine,^{276a} in the 2-position of pyridine,^{276b} and in the 2-, 4-, 5-, and 6-positions of pyrimidine²⁷⁷ (114) appears to be more reactive than chlorine. 2-Bromopyrimidine is stated to react with trimethylamine or cyanide ion much more rapidly²⁷⁸ than does the chloro analog. This relation is reminiscent of the behavior of halonitrobenzenes summarized by Bunnett: Cl > Br when ammonia or methylamine is the reagent; Br > Cl with other amines.^{261b} The fluoro substituent in 3-halopyridine *N*-oxides is extremely reactive compared to the chloro and bromo analogs.^{255b}

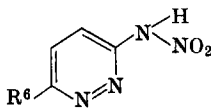
c. *Nitrogen*. (1) *Amino and substituted-amino* substituents are poor leaving groups but generally exceed hydroxy or oxo groups in reactivity. Acid catalysis sometimes results in a convenient degree of reactivity provided that several activating moieties are present. Curiously, the dimethylamino group is more reactive toward replacement by amine anions or acid-catalyzed amination than is the amino group; the methylamino group is intermediate in reactivity.¹⁴¹

2-Dimethylaminoquinoline is converted¹⁴¹ into the 2-amino analog by potassium amide (liquid NH₃, 20°, 18 hr). 4-Dimethylaminoquinazoline exceeds the methylamino derivative in reactivity toward ammonium acetate or alkali amides. Hot acid or alkali

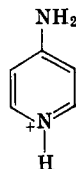
hydrolyzes²⁷⁹ the amino group in 2-aminoquinoline. 4-Aminopyrimidines react with amine acetates to give substituted aminopyrimidines (116)²⁸⁰; the 4-position is more reactive than the 2-position. 3-Amino-5,6-diphenyl-*as*-triazine²⁸¹ is hydrolyzed in good yield by hot alkali (100°, 4 hr). Amino or alkylamino groups on acridine,²⁸² cinnoline, quinazoline, and quinoline^{283a} are displaced by hydroxy groups in acid solution less readily than are chloro, alkoxy, alkylthio or phenoxy groups. 4-Anilino or alkylamino groups^{284a, 284b} on quinazoline and a 4-amino group on quinoline have been displaced by alkyl amines. The amino groups in 3,6-diamino-*s*-tetrazine are both readily replaced^{284c} with hydrazine (20°, < 4 hr). Pyrazole is the leaving group in the formation of 2-amino (or substituted amino)-*s*-triazine from 2-(pyrazol-1-yl)-*s*-triazine.^{284d}



[116]



[117]

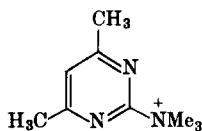


[118]

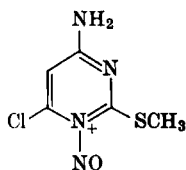
Some substituents such as the acylamino group are readily decomposed by many nucleophiles to give a poorer leaving group (e.g., amino). Others, such as nitroamino and sulfonylamino, are less reactive when they are anionized by the nucleophile. 3-Nitroaminopyridazine (117) and its 6-methyl derivative are readily aminated²⁸⁵ with benzylamine (130°, "short time"). 4,6-Dimethyl- and 6-methyl-2-nitroaminopyrimidine undergo 2-substitution^{286, 287} on warming a few minutes with hydroxylamine, hydrazine, primary or secondary alkylamines, or anilines.

(2) *Displacement of ammonio groups.* The acid-catalyzed displacements noted above presumably do not proceed via H_3N^+ —formation since amino-substituted heterocycles are usually protonated on the ring-nitrogen (118) and this form is more activated (see Section II, C). Ammonio groups are good leaving groups and the trimethylammonio group has a high reactivity in spite of its size. Other trialkylammonio groups are of much less significance as a result of greater steric hindrance (which sometimes prevents their formation) and instability (relative to reversal or to dealkylation by an anion or to rearrangement of an alkyl group to a ring-nitrogen).

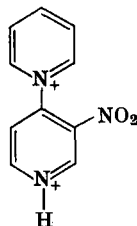
In benzene derivatives, the trimethylammonio group is highly reactive^{95,100}; it exceeds the reactivity of the nitro group by a factor of ten but its reaction rate is only one-fiftieth that of the dimethyl-sulfonio group. These rates are controlled by favorable entropies of activation since the activation energy of the last is 2 kcal *higher* than that of the other two. In heterocycles, the reactivity of the trimethylammonio group appears to be even greater and often exceeds that of chlorine. Reaction of 2-chloro-4,6-dimethyl- and 4-chloro-2,6-dimethyl-pyrimidine with potassium or cuprous cyanide failed, but displacement proceeded readily^{260a, b, 288a, 288b} with the Me_3N^+ analogs (119) prepared from them with trimethylamine. The quaternary salts were readily substituted by fluoride, cyanide, azide, hydroxide, alkoxide, or phenoxide ions. Other halides, phthalimide, and malonate ester anions demethylate rather than displace the group, presumably by aliphatic S_N2 attack at the methyl carbon. The quaternary salts undergo displacement with sulfonamide anions.^{289a} A benefit from indirect substitution resulted also in the case of 4-chloro-6-sulfanilamidopyrimidine which was much less reactive toward alkoxide ions (especially higher alkoxides) than was the 4-trimethylammonio



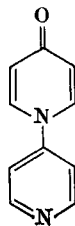
[119]



[120]



[121]



[122]

analog.^{289b} The sulfonamide anion of the substrate is formed under both reaction conditions, but its deactivating effect is substantially overcome by the cationic leaving group. Other 4-trimethylammonio-pyrimidines react with azide and fluoride ions.²⁹⁰ A 4-trimethylammonio group on 6-methoxy-^{263b} and 2,6-dimethoxy-pyrimidine^{288a, 288b, 289a} is far more reactive than a chloro group, even towards a nucleophile as bulky as the sulfanilamide anion; an explanation of this high reactivity has been proposed.^{263b} Some indication of the effect of charge is given by comparison of $-\text{NMe}_3^+$ and $-\text{CCl}_3$

which are comparable in size. The latter is unreactive to sulfanilamide anion but can be displaced by methoxide ion.

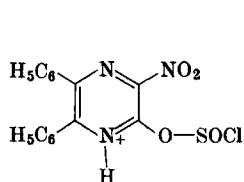
Although not isolated, there was some indication of the formation of "triethylammonio-*s*-triazines"²⁷¹ in cold ether from chloro-*s*-triazines carrying two other electron-withdrawing groups (Cl, Cl₃C, or Cl₂CH, but not ClCH₂). However, this possibility needs confirmation since the triethylammonio group cannot usually be introduced into other reactive positions in heterocycles.

A special type of ammonio group is represented by 4-(1-pyridinium)-pyridine and other azinium analogs.^{67,71} Such products often result from self-quaternization of highly reactive derivatives. *N*-(4-Pyridyl)- and *N*-(3-nitro-4-pyridyl)-pyridinium chloride hydrochlorides^{291a, 292a} (**121**) react with aniline, chloride ion, and water to give 4-substituted pyridines plus pyridine. 1-(2-Quinolyl)- and 1-(4-quinolyl)-pyridinium salts undergo 2- and 4-substitution, respectively, with amines, anilines, hydroxylamine, phenols, alkoxides, mercaptans, and chloride ion.^{291b}

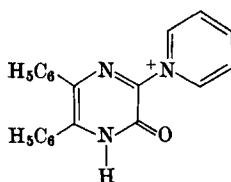
Attempted diazotization of amino groups *ortho* or *para* to an azine-nitrogen frequently leads to formation of the oxo ("hydroxy") analogs, as with 4-amino-6-chloro-2-methylthiopyrimidine,^{292b} and introduction of halogeno groups can sometimes be accomplished in high yield. For example, diazoniopyridazines (resulting from hypohalite oxidation of hydrazinopyridazines) in 5*N* acid rapidly give the chloro (75–95% yields) and bromo (40–65% yields) analogs^{292c}; in 5*N* sulfuric acid the oxopyridazines are obtained in 40–60% yields.^{292d} In concentrated hydrofluoric acid 2- and 3-fluoropyridines have been prepared^{292e} by diazotization of the amines. By diazotization of various 2-aminopyrimidines, 2-chloro- and 2-bromo analogs can be prepared.^{292f} Diazotization of 2-amino-1,8-naphthyridin-7-one in concentrated sulfuric acid produced the corresponding dioxo compound.^{292g} The mechanism of such reactions is not known, but the *S_N1* mechanism seems highly unlikely (cf. Section I, C, 2). Very probably an acid-catalyzed nucleophilic displacement takes place, the leaving group on the protonated or cationized azine ring being one of three possibilities: (a) —N₂⁺, (b) —NH—NO, or (c) the amino-immonium group in **120** formed by electrophilic attack on azine-nitrogen.

(3) *Nitro and azido*. In benzene derivatives, the *nitro* group is said to rival fluorine and exceed chlorine in replaceability.^{50, 71, 95, 261b} The reactivity of the nitro group in heterocycles is also very high, and this

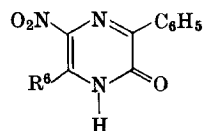
group certainly rivals the halogens in reactivity. Thus, 4-nitropyridine^{293,294} and its 3-methyl derivative²⁹⁵ self-quaternize and react with atmospheric moisture at 20° to give the corresponding 1-(4'-pyridyl)-4-pyridones (**122**) and also the 4-pyridones (presumably via acidic autocatalytic reaction, *nitric* acid being produced). The reactivity and dipole moments²⁹⁶ of nitropyridines have been discussed. The nitro group seems to be especially susceptible to acid-catalysis: 6-nitro-3-picolinic acid reacts with the weakly nucleophilic chloride ion at 0° (methanolic HCl or concentrated HCl) to give the 6-chloro ester or acid in high yield. Aqueous hydrochloric acid or alcoholic sulfuric acid gave the corresponding 6-pyridones. The nitro acid or ester reacted with methoxide ion apparently less readily than with chloride ion, and reaction with carbanions and NaNH₂ failed.^{297a} Facile displacements involving electrophilic catalysis have also been reported in pyrazines. The nitro group in 3-nitro-5,6-diphenylpyrazin-2-one is completely substituted^{223b} by a chloro group under the influence of thionyl chloride (**123**) or phosphorus oxychloride. Using thionyl chloride and pyridine (20°, 18 hr) or hydrogen chloride plus pyridine, the latter becomes the nucleophile and a 3-pyridinium compound (**124**) results.²⁹⁸ The 3-nitro group is quite reactive toward pyridine alone (100°, 1.5 hr), while the 3-chloro analog is stable. Under conditions giving anionization (e.g., in the presence of -OH or -OR), the 3-nitro group above is stable. The 5-nitro-3-phenyl and -3,6-diphenyl analogs (**125**) are stable^{223b} to the acid chlorides above, to acid, and to alkali. The nitro group is the more reactive in 2-halo-4-nitropyridines and their *N*-oxides toward hydroxide or alkoxide ions and toward ammonia.^{297b}



[123]



[124]



[125]

Relatively little work has been done on displacement of the *azido* group on benzenes^{261c,299} (by hydroxide, ammonia, amines, or hydrazine) or on heterocycles.^{300-302a,302b} The latter involve reaction of

2,4-diazidopyrimidines with ethoxide ions, the hydrolysis and amination of 2,4,6-tris-azido-*s*-triazine, and alkoxylation of 3-, 4-, and 5-azidopyridazine-1-oxides.

d. *N-Oxides and Their O-Derivatives*. The activation produced by these groups is discussed in Section II, C. As leaving groups they are almost unique in giving substitution at a different ring-position (*cine* substitution).

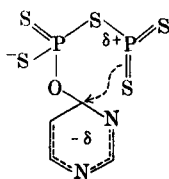
e. *Oxygen*. (1) *Alkoxy*. The methoxy group seems to be a poorer leaving group (Le) than methylthio on pyrimidine²⁶⁴ but not on *s*-triazine.^{303a} It is generally much less reactive than a chloro group, e.g., in 2-methyl- or 6-methoxy-4-Le-pyrimidines toward ammonia^{21c} or sulfonamide anions,^{263b, 264} but not in 2,5-dichloro-4-methoxypyrimidine toward methanolic ammonia.^{288b} At the elevated temperatures sometimes necessary for nucleophilic substitutions, the methoxy group is substantially demethylated while the methylthio group seems to be less susceptible to this side reaction. Trimethylammonio undergoes demethylation to a negligible extent, presumably because displacement occurs readily at moderate temperatures. With more activated methoxy groups, as in methoxy-*s*-triazines,^{303b-303d} displacement is predominant with a basic amine but only demethylation occurs with aniline at a higher reaction temperature. At a higher temperature, reaction is either less selective or more favorable to the aliphatic S_N2 reaction at methyl than to the S_NAr2 reaction at a triazine carbon. Thus, the demethylation reaction increases with low nucleophilicity of the reagent, with poor substrate reactivity, and with temperature elevation. Kukulja³⁰⁴ has found that demethylation of 6-benzylsulfonyl-3-methoxypyridazine by sulfanilamide anion predominates over methoxy displacement, whereas in our work²⁵⁴ with the methylsulfonyl analog the reverse was true. Dealkylation by sulfur nucleophiles (2-ethoxyquinoline with $C_6H_5S^-$) has been reported^{305, 306a} as has the displacement reaction. Some so-called hydrolyses of activated methoxyazines are probably demethylations via the aliphatic S_N2 mechanism, especially when a weak nucleophile or acid catalysis is involved. It has been observed^{306c} that the hydrolysis of ^{18}O -labeled 2-methoxypyrimidine with 2*N* sulfuric acid (100°, 4 hr) proceeds by the S_NAr2 mechanism to at least 90%.

Transetherifications of alkoxy and aryloxy heterocycles with alkoxides have been observed (Sections III, B and IV, B). In 2,4-dialkoxyquinazoline, only the 4-alkoxy group exchanges.^{306b} When 3-chloro-6-methoxypyridazine was treated with sodium alkoxides,

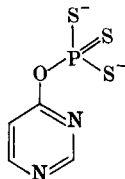
the displacement of the 3-chloro group occurred before transalkoxylation of the bis-alkoxy product.^{306d}

(2) *Aryloxy*, "*hydroxy*," *arylsulfonyloxy*, and *phosphoryloxy*. The 4-toluenesulfonyloxy and 4-nitrophenyloxy groups approximate the chloro group in replaceability in benzene derivatives.⁷¹ The former appears to be less reactive than chloro toward hydroxide on quinoline³⁰⁷ and 4-*phenoxy* on pyrimidine is relatively unreactive toward sulfanilamide anion or ammonia.^{288a, 308} On cinnoline, quinazoline, or quinoline, a 4-phenoxy group is less reactive^{283a} than a chloro group.

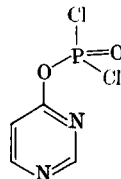
The replacement of a *heterocyclic* "*hydroxyl*" group (generally in the oxo form,³³¹ Section II, E, 2, e) with thioxo or chloro groups by phosphorus pentasulfide or phosphorus oxychloride presumably proceeds through nucleophilic substitution (frequently acid-catalyzed, **21** and **86**) of thiophosphoryloxy and dichlorophosphoryloxy intermediates. The 4-position in pyrimidine is more reactive than the 2-position and, at low temperature, this type of thionation of pyrimidine-2,4-diones is specific^{309, 310} for the 4-position. In *as*-triazine



[126]



[127]



[128]

-3,5-dione, 3-thionation is more difficult³¹¹ than reaction at the 5-position. This displacement, via structures **126** or **127** or the protonated form **21**, again shows the greater reactivity of a position *para* to one of the activating centers than of one *ortho* to both activating centers. Displacement in **128** as well as in the thionations may be intermolecular or intramolecular by the S_NAr2 mechanism. Replacement of a 4-oxo group on quinolines with a tolylthio group has been accomplished with tolylmercaptan^{247, 248a} at elevated temperatures (190°). 4-Amination of 4-hydroxy-2-quinolone with amines or their salts has been reported.^{312a}

Activated compounds such as 5-nitropyrimidin-2-one and 1-methyl-5-nitro-2-pyridone form the 2-chloro analogs with thionyl chloride^{223b, 312b} via displacement of the —O—SO—Cl group. In reactions

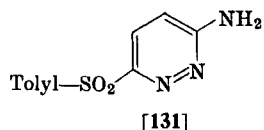
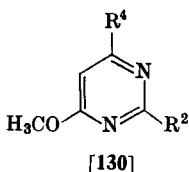
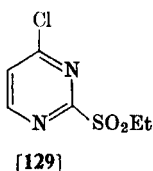
of azinones with acid halides where dimethylformamide is employed, e.g., in reaction^{312c} of a 2-substituted *as*-triazine-3,5-dione with thionyl chloride, the leaving group is probably $\text{—OCH(Cl)N(CH}_3)_2$. 5-(*p*-Toluenesulfonyloxy) appears to be the leaving group in the formation of 6-methyl-3-methylmercapto-5-pyridinium-*as*-triazine chloride from the 5-oxo analog and toluenesulfonyl chloride in pyridine; the pyridinium group was easily displaced by water, hydroxide ion, or azinone oxygen.^{312d}

f. *Sulfur*. Leaving groups attached to the ring through sulfur are very useful because of their degree of reactivity and their convenience of synthesis. Sulfonyl and sulfonio groups are the most reactive, but thioxo, substituted thio, sulfonate, and sulfamyl groups react with a variety of nucleophiles. Very little work has been done with sulfinyl^{67,71} as a leaving group. The reactivity of sulfonyl groups (RSO_2 -azine) appears to decrease with an increase in the size of R (alkyl or aryl). The 2-ethylsulfonyl group in **129** is less reactive³¹³ toward ammonia than is the 4-chloro group, and, in a related 2-methylsulfonyl pyrimidine,¹⁵³ the sulfonyl group is also less reactive toward sulfanilamide anion. This reactivity relation is more a function of the ring-position than of the leaving group since, in 2,6-dimethoxy-4-substituted-pyrimidines, the 4-ethylsulfonyl, 4-phenylsulfonyl, and 4-*p*-acetamidophenylsulfonyl derivatives react with sulfanilamide anion while the 4-chloro analog does not.

(1) *Alkyl- and aryl-sulfonyl*. Sulfonyl groups (RSO_2 —) are believed^{314,315} to withdraw electrons by resonance as well as by induction. Alkylsulfonyl heterocycles show far greater reactivity of this substituent than is indicated by Bunnett and Zahler's general order of displaceability^{261a} in which it is placed below halogen, aryloxy, alkoxy, aryl, and alkylthio. In some heterocyclic work it has been considered³¹⁶ roughly equivalent to the chloro group, but other studies indicate that it is more reactive.

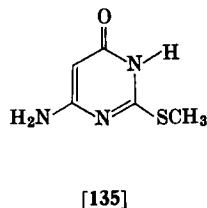
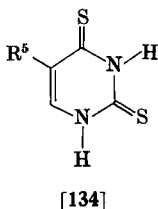
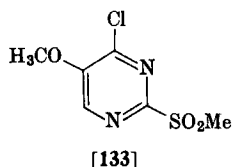
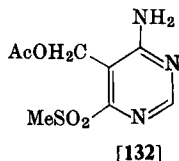
In work on 6-methoxypyrimidines (**130**), the 4-methylsulfonyl group was found to be displaced by the sulfanilamide anion more readily than were 4-chloro or trimethylammonio groups.^{263a} This reactivity may be partly due to the nature of the nucleophile (**106**, Section II, D, 1). However, high reactivity of alkyl- and aryl-sulfonyl heterocycles with other nucleophiles has been observed. A 2-methylsulfonyl group on pyridine was displaced by methoxide ion with alkaline but not acidic methanol.³¹⁷ 3,6-Bis(*p*-tolylsulfonyl)-pyridazine reacts (100°, 5 hr) with sulfanilamide anion and even the

deactivated 3-amino-6-(*p*-tolylsulfonyl)pyridazine (**131**) reacts (150°, 22 hr) with alkoxide ions.³¹⁸ In reactivity with hydrosulfide ion and in yield of product, **131** is at least equal³¹⁹ to that of the 6-chloro-analog. 3-Sulfanilamido-6-(*p*-tolylsulfonyl)pyridazine,³¹⁸ "deactivated" by anionization, seems to be about as reactive (150°, 12 hr) toward alkoxide ions as is the 6-chloro analog.³²⁰ In 3-chloro-6-methylsulfonylpyridazine the chloro group is preferentially displaced by sulfanilamide anion²⁵⁴ and by alkylamines and aniline.^{321a} However, in this substrate as well as in 4-chloro-6-methylsulfonylpyrimidine,^{321a} the relative reactivity involves their mutual activation as well as their mobilities as leaving groups.



Displacement of 2-ethylsulfonyl groups from various pyrimidines by amines, alkoxides, and hydroxide^{21d-f} has been reported. Substitution of the 2-ethylsulfonyl group with chloro was observed by Sprague and Johnson,^{321b} and of 2- and 4-methylsulfonyl with chloro or dialkylamino by Noell and Robins.³¹⁶ The 2-methylsulfonyl group was said³¹³ to resemble a chloro group in the ease of replacement by hydroxide, ethoxide, and ammonia. In 4-RSO₂-pyrimidines (R = CH₃,^{263,264} C₂H₅,³²² C₆H₅,³²² C₆H₅CH₂³²³) deactivated by 6-methoxy or 2,6-dimethoxy groups (**130**), displacement by sulfanilamide anion is still facile (60°, 15 min). Another example of the reactivity of the sulfonyl group overcoming deactivation by other substituents is the reactivity of 5-acetoxymethyl-4-amino-6-methylsulfonylpyrimidine (**132**) with ammonia or amines.³²⁴ The superior reactivity^{309,324} of a methylsulfonyl group over a chloro group is clearly evident from the fact that the usually higher reactivity at the 4-position is sometimes overcome by methylsulfonyl at the 2-position. 2-Substitution of 4,6-dichloro-2-methylsulfonylpyrimidine by excess ethyleneimine (< 45°, < 1 hr) in benzene³²⁵ is illustrative. Differential deactivation (Section II, E) rather than relative reactivity of the leaving group determines the site of reaction in the following: displacement¹⁵³ of only the chloro group from 4-chloro-5-methoxy-2-methylsulfonylpyrimidine (**133**) with sulfanilamide anion in dimethylsulfoxide (0.5 hr at

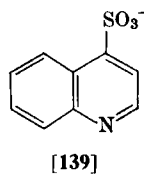
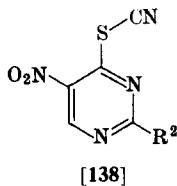
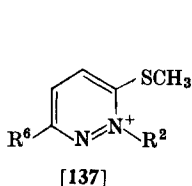
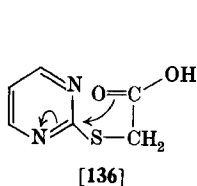
65°); 4,5-dimethoxy-2-methylsulfonylpyrimidine with sulfanilamide anion in molten acetamide (2.5 hr at 90°) gave a 2:1 ratio of 4- to 2-displacement.¹⁵³



(2) *Alkylthio, arylthio, and thioxo*. The thioxo group in pyrimidine-2,4-dithione can be displaced by amines,³²⁶ ammonia,³²⁷ and amine acetates,³²⁸ and this amination is specific for the 4-position in pyrimidines and quinazolines. 2-Substitution fails even when a 5-substituent (cf. **134**) sterically prevents reaction of a secondary amine at the 4-position. Acid hydrolysis of pyrimidine-2,4-dithione is selective³⁰⁹ at the 4-position. 2-Amination of 2-thiobarbituric acid and its *S*-methyl derivative has been reported.³²⁹ Under more basic conditions, anionization of thioxo compounds decreases the reactivity: 2-thiouracil is less reactive^{330a} toward hot alkali than is the *S*-methyl analog. Hydrazine has been reported^{330b} to replace (95°, 6 hr, 65% yield) the 2-thioxo group in 5-hexyl-6-methyl-2-thiouracil. *Ortho* and *para* "mercapto-" or "thio-" azines are actually in the thione form.³³¹

A 2-methylthio group on 4-pyrimidinones and on 6-amino-4-pyrimidinones (**135**) is displaced²⁸⁰ by methylamine acetate and by various salts of ammonia and other amines.^{332, 333} Similarly, substitution by hydroxy groups^{334, 335} occurs in hot aqueous acid with 2-arylthio- or -alkylthio-pyrimidines. Methylthio appears to be a better leaving group than a methoxy group on pyrimidine²⁶⁴ but not on *s*-triazine.^{303a} A 2-methylthio group on pyrimidine is stable to many nucleophiles (NH₃, ⁻OCH₃, CH₃NH₂) but can be displaced by

hydrosulfide³³⁶ under certain conditions, even in the presence of deactivating substituents. Carboxymethylthio groups are easily hydrolyzed, possibly via an intramolecular S_NAr2 mechanism (136) or by intermolecular bifunctional catalysis^{218, 227} (Section II, C).



Alkaline hydrolysis³³⁶ of 6-methoxy-4-methoxycarbonyl-2-methylthiopyrimidine leaves unaffected only the methylthio group which can then be hydrolyzed in acid. 9-Alkylthioacridines²⁸² are hydrolyzed by acid less readily than the corresponding alkoxy compounds and more readily than alkylamino derivatives. Peculiarly, a better yield of the amine results from 4-thioxo than from 4-methylthio-quinazoline on heating with primary amines.^{337a} Displacement in 2-methylthio-quinolinium^{54f} and 3-methylthiopyridazinium compounds (137)²³⁵ proceeds readily with the carbanion of diethylmalonate or the zwitterion of 2-methylbenzothiazolinium derivatives.

4-Arylthio but not 2-arylthio groups in quinazolines can be replaced with hydroxide ion or alkylamines.^{284a} 4-Alkylthio-2-alkyl (or aryl)-quinazolines are readily alkoxyated (65°, 1 hr, 80–90% yield) at the 4-position.^{337b} Arylthio and alkylthio groups have been found to be poorer leaving groups than chloro in several azines.

4-Thiocyanato groups in pyrimidines (138 where R² is chloro or amino) have been replaced with amines, ethoxide ion, phenoxide ion, and thiourea.³³⁸

An acylthio group appears to be the leaving group in the reaction of 2-thioxopyrimidines with phosgene (102°, 3 hr) to form 2-chloro derivatives in high yield.^{337c} Thiouronium (guanylthio) is the leaving group in the formation of a di-4-pyridylsulfide^{337d} from 2,6-dicarboethoxy-4-thiouroniumpyridine and the related 4-thioxo compound (formed *in situ*).

(3) *Sulfonate and sulfamoyl*. A nitrile group is introduced into the 3- or 4-position of pyridine^{341–343} and into the 2- or 4-position of pyrimidine²⁶⁵ by displacement of a sulfonate group with potassium cyanide. Amines, water, or hydrazine displace 2- or 4-sulfonate groups from pyridine derivatives.^{339, 340} 4-Quinolinylsulfonates³⁴¹ (139)

(prepared readily from the corresponding chloro compounds) react better²⁰³ with ammonia and amines than do the chloro analogs. A 3-sulfo group in pyridines can be replaced with a carboxyl group using *anhydrous* sodium formate.³⁴³

(4) *Sulfonio*. Incorporation of this group in azines may present synthetic and stability problems. In benzene derivatives, dimethyl-sulfonio⁹⁶ is substantially better as a leaving group than is a nitro or trimethylammonio group.

E. ACTIVATION AND DEACTIVATION BY OTHER GROUPS

1. General Effects and Summary

The effects of nuclear substituents other than the leaving group on nucleophilic substitution of azines and on their relative positional reactivity are illustrated by selected examples. In most instances, these effects apply to both azines and carbocyclics, as would be expected from a theoretical consideration of the nature of the effects. Generally, activating substituents are also good leaving groups and deactivating ones are poor leaving groups. Electron-donors slow aromatic nucleophilic substitution by increasing its energy of activation, while electron-attractors speed it by lowering the energy of activation (cf. Sections I, D, 2, f; III, A, 2; and IV, A, 2); both influences can involve conjugation (electron-transfer) and induction (electron-cloud deformation). The designation "*ortho*- and *para*-directing substituents" as customarily used applies only to electrophilic substitutions. The so-called "*meta*-directing substituents" as a class are activating for nucleophilic substitutions taking place in the *ortho*- and *para*-positions relative to them (less so for *meta*-positions), while the former class is generally deactivating, with certain exceptions such as the halogens.⁵⁴¹

In aromatic nucleophilic substitution, relative rates are frequently determined by entropies of activation which sometimes cause the greatest reactivity in the least activated member of a series. The greater effectiveness of activation or deactivation (changes in activation energy) when operating from the *para*-position than from the *ortho*-position will be apparent from the examples below. Relative positional reactivity can be altered by electrostatic effects in the ground or transition states and by hydrogen bonding in the transition state (cf. Sections I, D, 2, a, I, D, 2, b, and III, A, 2). The effects of substituents in carbocycles have been reviewed by Bunnett and

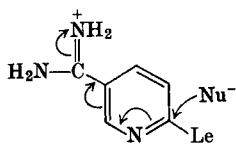
Zahler^{54d} and elaborated in a series of papers by Miller and co-workers^{80a, 80b} and in Bunnett's publications, many of which are cited in Section I, D. It should be pointed out that the effects of substituents on nucleophilic substitutions show important differences from their effects on other reactions or on equilibria which involve competition for a lone-pair of electrons on another group or stabilization of negative charge on some atom of the reacting moiety. The σ -constants for nucleophilic substitutions differ from those determined in the latter work in that they show the response of the substituent to a strong demand for stabilization of negative charge on the substituent itself, especially by resonance.

The effect of another group on the reactivity of a substituted azine sometimes complicates conclusions as to the relative reactivity at different ring-positions. In polysubstituted compounds, such as 2,4-dichloropyrimidine, the mutual activation of the chlorines is not equal in general. More obscure is the complex result of insertion of a group (e.g., in 6-amino-2,4-dichloropyrimidine) which deactivates the ring, again in general unequally at different positions. The net reactivity pattern from this combined effect of relative positional reactivity, of mutual activation by potential leaving groups, and of deactivation or activation by other substituents is often hard to predict.

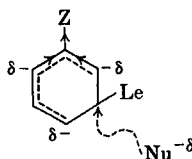
In polysubstituted carbo- and hetero-aromatics, most nucleophilic substitutions produce a step-by-step decrease in the displaceability of the remaining substituents. This progressive decrease is a general consequence of the entering group being a better nucleophile (electron donor) than the leaving group. An exception to this general rule is the substitution of a chloro group by a trimethylammonio group, which leads to an activating effect on the remaining chloro groups.

Substituents are unlikely to inhibit sterically the activating resonance of azine-nitrogens, as sometimes occurs in nitro-carbo-aromatics. The principal electronic effect of an aromatic substituent is to stabilize or destabilize the incipient negative charge on the ring in the transition state (cf. Section II, A, 1). A positive atom in the substituent can activate by induction, but its activation is much greater if a locus for neutralizing the negative charge is provided, for example, a diazonium (**15**) or amidinium group (**140**) vs. an external ammonium group (azine—⁺NR₃). In the transition state, the incipient negative charge on the ring may also be dispersed over appropriate atoms of a substituent and the resonating system thereby enlarged

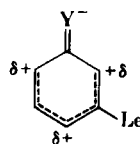
and stabilized. Most activating substituents produce an electron shift in the direction of the transition state by electron withdrawal in the ground state, but this effect seems clearly to be less significant than the ability to stabilize the transition state by resonance; for example, Me_3N^+ is less activating than a nitro group. Anionic activating groups (e.g., COO^-) are presumably not electron-withdrawing in the ground state but activate by assisting resonance stabilization of the ring's negative charge in the transition state. An electron-attracting substituent in the *meta*-position can stabilize the transition state by inductive electron attraction (141), either along the σ -bonds or directly through space.³⁴⁴ By means of an "inductive" resonance



[140]



[141]



[142]

effect, certain substituents in a *meta*-position stabilize the transition state and intermediate complex by tending to place a positive charge (142) where the nucleophilic substitution of a leaving group (Le) tends to place a negative charge. Resonance parameters proposed by Taft and co-workers^{179, 345} for *meta* groups assign definite values to this effect in benzene derivatives.

The Hammett equation has been applied to azines in various studies,³⁴⁶⁻³⁴⁸ and σ -values have been predicted for various positions in azines.³⁴⁹ However, applicability to *ortho*-substituted heterocycles may require a modified equation since reactions of *ortho*-substituted compounds or of those bearing electrically charged groups⁹³ often do not have the proportional changes of entropy of activation required for valid application of the usual Hammett equation. Its application to nucleophilic substitution of carboaromatics¹⁶⁵ bearing conjugative substituents requires the introduction of σ^* - and σ_{Nu}^{**} -values. The empirical additivity rule for the free energy of activation has been reviewed by Jaffé.^{268b} In several series, the effect of substituents in polysubstituted compounds can be expressed as the sum of the individual effects in the monosubstituted analogs. The heterocyclic work cited herein qualitatively demonstrates the general principle of

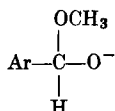
the additivity of substituent effects. Stone and Pearson³⁵⁰ proposed that steric hindrance to solvation of the transition state was the cause of certain exceptions to additivity in electrophilic reactions. They pointed out that, as regards this effect, nucleophilic reactions are probably less sensitive to the bulk effect of substituents in producing non-additive results. Additivity applies also to the opposing actions of activating and deactivating groups. Schubert *et al.*³⁵¹ have discussed the limitations of the static viewpoint of assigning a permanent electron-donor character to alkyl substituents and certain general aspects of the discussion are applicable to substituents in general. Jaffé and Jones³⁵² have discussed applications of the Hammett equation to heterocycles.

The effect of a substituent on aromatic nucleophilic substitution can vary with:

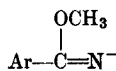
- a. its position relative to the leaving group (Le) as regards
 - (1) activation or deactivation towards attack by the nucleophile (Nu),
 - (2) London forces acceleration^{51, 52, 117b} when the substituent is *ortho* to Le,
 - (3) electrostatic interactions or hydrogen bonding to Nu or to Le in the transition state ("ortho effects"),
 - (4) steric hindrance; probably only significant with very bulky nucleophiles,
- b. its position relative to ring-nitrogen (indirect deactivation),
- c. its position relative to π -electronic dissymmetry of bicyclics,
- d. its anionization (e.g., $-\text{OH}$ or $-\text{COOH}$ vs. $-\text{O}^-$ or $-\text{COO}^-$) or cationization (e.g., imino or amino vs. $=^+\text{NH}_2$ or $=^+\text{NH}_3$),
- e. its hydrogen bonding to the solvent or to the reagent (e.g., *N*-oxide, imino, oxo, amino, anionic hydroxy, carboxy, or sulfonate substituents), and
- f. its concurrent interaction with Nu or an electrophile associated with Nu.

The effect of a substituent may be substantially modified by fast, concurrent, reversible addition of the nucleophile to an electrophilic center in the substituent. *Ortho*- and *para*-CHO and *para*-CN groups have been found by Miller and co-workers⁹⁴ to have a much reduced activating effect on the displacement of halogen in 2-nitrohalobenzenes with methoxide ion [reversible formation of hemiacetal (143) and imido ester anions (144)] than with azide ion (less interaction) or thiocyanate (little, if any, interaction). Formation of *O*-acyl derivatives of oxo derivatives or of *N*-oxides,^{353a} hydrogen bonding to these moieties, and ionization of substituents are other examples of reversible and often relatively complete modifications under reaction conditions. If the interaction is irreversible, such as hydrolysis of a

cyano to a carboxamido group or of an acylamino to an amino group, the rate of this interaction will determine whether the initial or final substituent affects the rate of nucleophilic substitution. The relative reactivity of cyano and chloro groups in 2-chloro-3- or -5-cyanopyridines^{353a} seems to depend upon whether reversible (CH_3O^-) or irreversible (H_2O) addition of the nucleophile to the cyano group takes place.



[143]



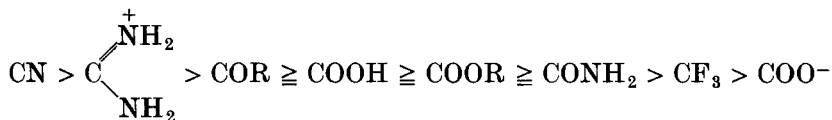
[144]

Activation by substituents is generally in the order *para* > *ortho* > *meta* unless a specific "ortho effect" intervenes. However, electrostatic or hydrogen-bonding interaction with an adjacent substituent can alter the relative reactivity at positions *ortho* or *para* to an azine-nitrogen (cf. Sections I, D, 2, a and I, D, 2, b). These interactions are usually characteristic of activating substituents. When activation is produced by a substituent such as a nitro group in addition to one or more ring-nitrogens, the relative reactivity will be determined by azine reactivity factors plus hydrogen-bonding effects associated with the substituent. Thus, one can expect 3-nitro-2-substituted-pyridines and analogous azine derivatives to be more reactive than 5-nitro-2-substituted-pyridines with amines but less reactive with anionic nucleophiles.

When a positively charged substituent such as the trimethylammonio group is anywhere on the ring, but most effectively when it is *ortho* to the leaving group, it can favorably affect the entropy of activation with anionic nucleophiles⁹³ and accelerate reaction. A recent example of reagent-substituent interaction is the electrophilic substitution of 2-carboxybiphenyl, nitration (non-polar solvent) of which occurs only at the 2'-position and not the 4'-position and has been postulated^{353b} to be due to the interaction of the nitronium ion with the carboxyl group.

In aromatic nucleophilic substitution, two general effects of substituents are (1) to alter the ground state in a direction toward or away from the transition state and (2) to withdraw electrons from or donate them to the pentadienoid anion in the transition state and

intermediate complex. The activating substituents are of the following types: (a) attached through carbon:



> C_6H_5 (sometimes weakly deactivating¹⁰³); (b) "halogen": $\text{IO}_2 > \text{CF}_3 > \text{Br} > \text{Cl} \cong \text{I} > \text{F}$ (the last is slightly deactivating); (c) attached through nitrogen: $\text{N}_2^+ > \text{NO}_2 \sim \text{NO} > \text{R}_3\text{N}^+ > \text{N}_3$ (the last is slightly deactivating in terms of E_A but slightly activating in terms of the rate^{353c}); (d) attached through oxygen: OSO_2R , OPOX_2 , OPS_3H_2 , O -acyl, ring carbonyl or thiocarbonyl (cf. true hydroxy and mercapto groups below); (e) attached through sulfur: $\text{R}_2\text{S}^+ > \text{RSO}_2 > \text{SO}_2\text{NH}_2 > S$ -acyl $> \text{SO}_2\text{NH}^- > \text{SO}_3^- > S$ -Ar $> S$ -alkyl $\cong \text{SH}$ (unionized); and (f) attached to ring-nitrogen: Ar, H, alkyl, O (*N*-oxide), $\text{N}-\text{OZ}$ (Z is an electrophile such as CH_3CO or POCl_2), $\text{N}-\text{Z}$. Group *f* is treated in Section II, C. In work on *s*-triazines (cf. Section II, B, 4, c and ref. 576b), the dialkyl phosphonate group [$-\text{PO}(O\text{-alkyl})_2$] appeared to be electron-withdrawing with respect to the chloro group. Deactivating substituents are the following: NR_2 , NH_2 , O^- , S^- , RSO_2N^- , true OH, O -alkyl, O -Ar, alkyl. The activating and deactivating relations discussed herein are derived from kinetic data on aromatic nucleophilic substitutions except in a few cases where estimates were made. The effect of the alkylmercapto group is variable, activating both electrophilic and nucleophilic substitutions. Groups having an anionic atom attached to the ring ($\text{RSO}_2\text{N}^- < \text{S}^- < \text{O}^-$) are more strongly deactivating (due to ground state conjugation with the electron-attracting ring and to transition state conjugative and inductive electron donation) than their unionized analogs while those with the charge farther removed are often activating (SO_3^- , COO^-). Anionic oxygen ($\text{Ar}-\text{O}^-$) is more deactivating than a neutral alkoxy group. The deactivating effect of certain groups (e.g., HO, RO, NH_2 , and NR_2) may be significantly altered when they are solvated with a protic solvent and, therefore, become less electron-donating. Their deactivating effect is more completely overcome by protonation (usually on a ring-nitrogen) in acid-catalyzed nucleophilic substitutions. Hydrogen-bonding solvation of an anionic group will tend to make it less deactivating.

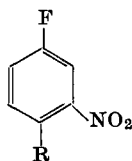
The information in Table I is condensed from Bunnett and Zahler's review.^{54d} Activating groups in order of decreasing activating

power are: N_2^+ , azinium N^+-R , NO , NO_2 , azine- N , SO_2Me , $+NMe_3$, CN , acyl, CF_3 , $COOH$, SO_3^- , halogeno, COO^- (weak), phenyl (variable). The magnitude of the increase in the rate of nucleophilic substitution (piperidino-dehalogenation or methoxy-dehalogenation) produced by the presence of an activating group in 4-substituted halobenzenes is essentially the same as in 4-substituted 2-nitrohalobenzenes^{54d} (Table I). However, the magnitude of the activating

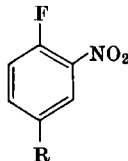
TABLE I
APPROXIMATE RELATIVE RATES OF HALOGEN DISPLACEMENT
FROM 4-SUBSTITUTED HALOBENZENES AND 4-SUBSTITUTED
2-NITROHALOBENZENES

Substituent	Approximate relative rate	Substituent	Approximate relative rate
NO_2	170,000	F	0.25
$MeSO_2$	18,000	Alkyl	0.2
Me_3N^+	5,500	Alkoxy	0.02
CN	5,000	Dialkylamino	0.001
$MeCO$	2,000	Hydroxy (ionized)	0.0007
Cl, Br, I	5-10	Amino	0.0001
COO^-	2		
H	1		

effect of a chloro group in the less activated **145** was 1.5-2-fold greater than in **146** for their respective methoxy-defluorination.³⁵⁴ Substituents in the 4-position are generally considered to give rates more indicative of their electronic effect on the reaction because of the absence of "ortho effects" and of steric hindrance. Bunnett and Zahler^{54d} considered that every substituent *ortho* to the reaction site has some steric effect on the rate.

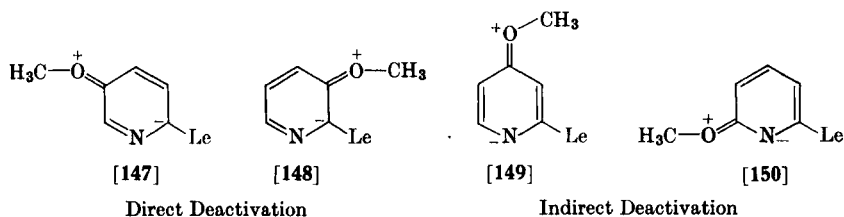


[145]



[146]

Direct deactivation results from an electron-donating atom or an anionic atom, which is *ortho* or *para* to the leaving group (Le), supplying electrons by resonance to the site of substitution in the ground state and, probably less so, in the more negatively charged ring of the transition state. *Indirect deactivation* by a group *meta* to the leaving group is produced by similarly supplying electrons by resonance in both states to the activating azine or azinium center which must bear the major share of the negative charge generated by nucleophilic substitution. Direct deactivation of nucleophilic substitution by ring substituents will be greater when the electron-donating substituent is *para* (147) to the site of substitution than when it is *ortho* to it (148). Indirect deactivation will likewise be greater when the electron donor is *para* (149) to the activating ring-nitrogen than when it is *ortho* to it (150). The generally greater basicities^{355, 356a} of 4-methoxy-, 4-chloro-, and 4-amino-pyridines and of 4-amino hetero-

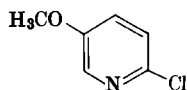


cycles than of the corresponding 2-substituted compounds is a reflection of greater electron donation from the 4-position although there is also an unfavorable field effect at the 2-position. The $n \rightarrow \pi^*$ electronic absorption spectrum^{356b} can give a measure of this electron donation by a substituent on an azine. Direct deactivation is stronger than indirect, when both are *para* or both are *ortho*. However, there is some evidence that *para* indirect deactivation (cf. 149) is more effective than *ortho* direct deactivation (cf. 148). Both kinds of deactivation will generally be greater when the substituent atom attached to the ring is negatively charged than when it is uncharged. The generalization that reactions favor a "*para*-quinoid" transition state is illustrated by the fact that electrophilic substitution occurs predominantly in the *para*-position of phenols, phenyl alkyl ethers, anilines, etc. The effect of a substituent's ring-position on deactivation of nitrohalobenzenes has been studied by Miller and co-workers.^{96, 357a}

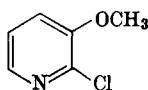
The methoxy or amino derivatives of various chloroazines provide

structures suitable for (a) comparing direct with indirect deactivation, (b) evaluating the effect of a combination of both, and (c) determining the influence of the location of the deactivating substituent. However, critical comparisons of the reactivity of such compounds are not available; qualitative indications are discussed under "methoxy" or "amino" below. Deactivation of a moderately activated chloroazine by a substituent may involve the same decrease in rate and elevation of activation energy as deactivation of a highly activated analog, but the disappearance of useful reactivity in the former often seems like a more drastic change.

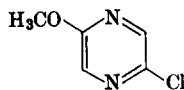
Direct deactivation in the methoxychloropyridines can be *para* (cf. **151**) or *ortho* (cf. **152**). It is to be expected that *ortho* direct deactivation of the more reactive 4-chloro-3-methoxypyridine will leave



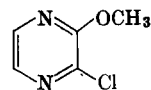
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[153]



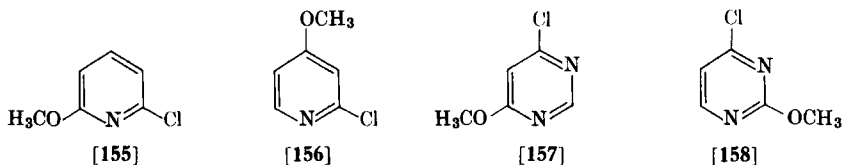
[154]

greater residual reactivity than it will in the less reactive 2-chloro isomer (**152**). Direct deactivation in some diazines is necessarily associated with indirect deactivation of an "inductive" ring-nitrogen. For example, in 2-chloro-5-methoxypyrazine (**153**) and in the isomeric 3-chloro-6-methoxypyridazine there is *para* direct deactivation and *ortho* indirect deactivation, respectively, via electron donation by the methoxy group to a ring-nitrogen. In 2-chloro-3-methoxypyrazine (**154**) and in 3-chloro-4-methoxypyridazine, the methoxy group exerts *ortho* direct deactivation plus indirect deactivation of the "inductive" azine-nitrogens. When the deactivating effect of a 2-amino group is imposed on the symmetrical molecule 3,5-dibromopyrazine, an overwhelming dissimilarity in the two leaving groups is produced. With a variety of nucleophiles, 60–97% yields of 3-substitution products are isolated.^{357b}

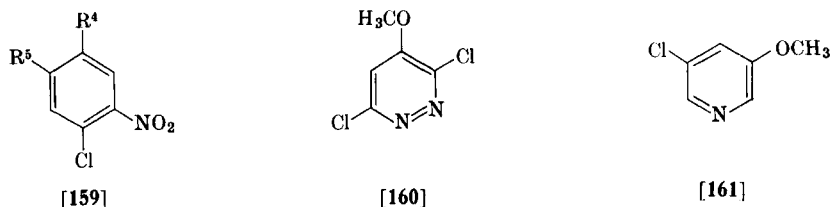
Comparison of the *ortho* and *para* indirect deactivation in **155** and **156** with that in **151** and **152** would reveal the relative effectiveness of the two effects and the influence of the ring-position. Additional examples of deactivation are: *ortho* indirect in 2-chloro-6-methoxypyrazine; *ortho* direct in 4-chloro-5-methoxypyrimidine; *para* direct in 2-chloro-5-methoxypyrimidine; *ortho* and *para* indirect in the

pyrimidine **157**, in 2-chloro-4-methoxypyrimidine, and in 2-chloro-4-methoxy-*s*-triazine; and doubly *ortho* indirect in **158**.

The negatively charged ring in the transition state and intermediate complex presumably exerts little or no inductive electron attraction on a substituent. So, as one might expect, the transition-state effect of an azine methoxy group can differ from its (conjugated)



ground-state effect. It can inductively stabilize the transition state relative to hydrogen (anisole is polarized toward its electron-withdrawing methoxy group in its ground state). The electron-withdrawing action of a *meta* methoxy group is reflected in a positive σ -constant^{268b} for many reactions of benzene derivatives. In piperidino-dechlorination of 2-nitrochlorobenzenes,³⁵⁸ 5-methoxy and 5-ethoxy groups (cf. **159**) increased the rate as a result of decreased energy of activation, in spite of the *para* indirect deactivation possible. In methoxy-dechlorination¹⁰² of the same substrate, a 5-methoxy group gave about three times the rate of the 5-methyl or hydrogen analog.



This electron-withdrawing action of a methoxy group can oppose the deactivating effect in structures such as **155** and **156**. One might conclude from the behavior of **160** that such inductive activation is not great enough to overcome the difference in deactivation: the 3-chloro group (*ortho* direct deactivation) is more reactive³⁵⁹ toward methoxide than is the 6-chloro group (*para* indirect deactivation). This relative reactivity illustrates greater deactivation when it is *para* indirect (on 6-chloro) than when it is *ortho* direct (on 3-chloro). This relation of deactivation effects also holds for 4-amino- and for

anionic 4-sulfanilamido-3,6-dichloropyridazines^{359,360} in their reaction with methoxide ion. The significance of deactivation in determining these superior reactivities at the 3-position is indicated by the fact that the 4-methyl analog reacts with alkoxide ion^{361a} and with sulfanilamide anion³²⁰ about equally at both chlorines. The inductive effect could be evaluated in **161** where the methoxy group is *meta* to the leaving group and to the ring-nitrogen by comparison with the reactivity of 3-chloropyridine. In other azines, such inductive activation by methoxy or other groups is not possible without simultaneous indirect deactivation since they will be either *ortho* or *para* to a ring-nitrogen.

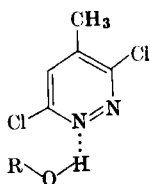
2. Nuclear Substituents

These are arranged alphabetically according to the atom attached to the ring (C, halogen, N, O, S) and under each atom by the name of the group. To facilitate comparison of the effects of substituents both as leaving groups and as activating or deactivating substituents, the subdivision and arrangements of this section and of Section II, D, 2 are the same.

a. *Carbon.* (1) *Alkyl, substituted-alkyl and aryl substituents.* Alkyl substituents are moderately deactivating in nature while the phenyl group is less so and, in some instances, is slightly activating. Substituted-alkyl groups become less deactivating the more electron-attracting substituents are present therein and the closer the latter are to the azine ring (as to deactivation, $\text{Cl}_3\text{C} < \text{Cl}_2\text{CH} < \text{ClCH}_2 < \text{ClCH}_2\text{CH}_2 < \text{CH}_3\text{CH}_2$); the α,α -dihalo- and perhalo-alkyl groups are activating. The triphenylmethyl group is like hydrogen in its effect on the *N*-alkylation of pyridines.^{361b} It is presumed that an *ortho* or *para* carbonium ion will be activating as a result of resonance stabilization of the partly anionic transition state. An enamino or amino-alkylene group ($\text{R}_2\text{N}-\text{CH}=\text{CH}-$)^{361c} is a special type of alkyl group, which is deactivating as expected.

The deactivating effect of *methyl groups* in 2-chloro-4-methyl- and in 4-chloro-2-methyl-pyrimidine causes a 2.5-fold decrease in the rate¹⁶⁷ of alkylamino-dechlorination (cf. Table III, p. 272). In piperidino-dechlorination³⁵⁸ of 2-nitrochlorobenzenes (**159**), a 5-methyl group has only a slight indirect deactivating effect while a 4-methyl group causes a 7-fold decrease in the rate (activation energy effect only). A 4-*phenyl group* doubles the rate, while a 5-phenyl group produces no change relative to hydrogen.

In the reaction of 3-chloropyridazines with sulfanilamide anion, a 6-methyl group decreases the reactivity²⁵⁴ relative to a 6-chloro group. Comparison of *ortho* direct deactivation of a 3-chloro group and *para* indirect deactivation of a 6-chloro group by a methyl group is possible in 3,6-dichloro-4-methylpyridazine, but the relative reactivity seems to depend on the size of the nucleophile (large RO⁻ favors substitution at the 6-position, due to the steric effect of the 4-methyl group) and on hydrogen bonding (**162**) of the solvent to the substrate at the more basic 1-nitrogen (hydrogen bonding adjacent to the 6-chloro group favors substitution at the 3-position^{320, 361a, 362}).



[162]

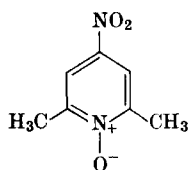
Aqueous acidic or alkaline reactions give equivalent or predominant amounts of 3-substitution (with HO⁻, N₂H₄, AcO⁻, H₂O, or sulfanilamide anion). On the other hand, reactions with hydrazine^{292d} or ammonia in alcohols or benzene give a great predominance of 6-substitution.

The effect of *alkyl substituents* on chemical and electronic transition and ground states has been recently summarized by Schubert *et al.*³⁵¹ Alkyl groups have generally been considered to have hyperconjugative or inductive effects or both. Alternative theoretical interpretations by Dewar and Schmeising^{119a, b} and new data^{363, 364} on solvent influences on the effect of substituted alkyl groups in electrophilic reactions (Baker-Nathan effect) have removed the theoretical and principal experimental support for hyperconjugation as previously regarded. The static viewpoint of a permanent electron donation by alkyl substituents (relative to H) does not predict that *p*-alkyl substituents would lower the energy of the ("nucleophilic") principal electronic transition³⁵¹ of phenol, aniline, etc., which involves acceptance of electrons or some equivalent process. Still another theoretical interpretation, based on non-bonded interactions, of the experimental effects ascribed to hyperconjugation has been made by Bartell.¹²⁰

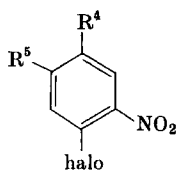
The *ortho* indirect deactivating effect of the two methyl groups in 2,6-dimethyl-4-nitropyridine 1-oxide^{252a} (**163**) necessitates a much higher temperature (about 195°, 24 hr) for nucleophilic displacement of the nitro group by chloride (12*N* HCl) or bromide ions (5*N* HBr) than is required for the same reaction with 4-nitropyridine 1-oxide (110°). With 5-, 6-, or 8-methyl-4-chloroquinolines, Bailey³⁶⁵ observed 2–7-fold decreases in the rate of piperidino-dechlorination relative to that of the des-methyl parent (cf. Tables VII and XI, pp. 276 and 338, respectively).

The *para* direct deactivation (toward excess piperidine, 45°) by a 4-methyl substituent on 2-nitrobromobenzene (**164**) is greater³⁶⁶ than *para* indirect deactivation by a 5-methyl group (rate of displacement equivalent to absence of a methyl group). A similar result¹⁰² was obtained with 2-nitrochlorobenzenes substituted by methyl or methoxy groups in the reaction with piperidine in benzene.

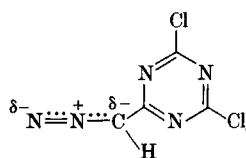
2-Amination³⁶⁷ of the deactivated carbanion of 4-benzylpyridine formed with excess sodamide presumably proceeds because the strong indirect deactivation is overcome by electrophilic attack by Na⁺ at the partially anionic azine-nitrogen and by concerted nucleophilic attack by H₂N⁻ at the 2-position via a 6-membered cyclic transition state (**75**). However, in simple nucleophilic displacement a carbanion will be more deactivating than the corresponding alkyl group, as is true in general for anionic substituents and their non-ionic counterparts.



[163]



[164]



[165]

The *diazomethyl* group in **165**, formed from 2,4,6-trichloro-*s*-triazine and diazomethane,³⁶⁸ deactivates (relative to chloro) the remaining chloro groups towards diazomethane, ammonia, and methoxide ion.

The deactivating effect of a *phenyl* group relative to a CCl₃ group on *s*-triazines is noted below,²⁷¹ but comparison with hydrogen as a substituent does not appear to have been reported in heterocycles.

Trihalomethyl, perhaloalkyl, and α,α -dihaloalkyl groups are discussed under halogens below.

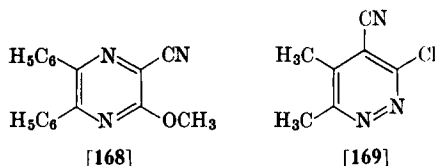
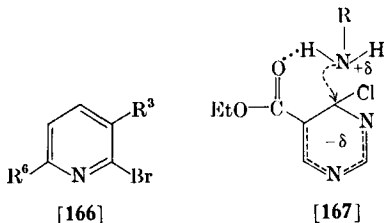
(2) "*Carboxyl-related*" and *acyl substituents*. Included here are cyano, protonated amidinium ion, thionoacyl, acyl ($\text{Ar}-\text{CO}$, $\text{H}-\text{CO}$, $\text{Alkyl}-\text{CO}$), carboxamido, carboaryloxy, carboalkoxy, carboxy (unionized), amidino (unionized), and carboxylate anion, listed approximately in order of decreasing electron attraction or activation. The relative activation by some of these groups (e.g., ketone, aldehyde, nitrile) will change upon reversible interaction with the nucleophile, which will vary with the group and with the nucleophile⁹⁴ (e.g., MeO^- , N_3^- , NCS^-). Irreversible interaction will be obvious when the reaction products in kinetic studies are characterized.

Alteration of positional selectivity will result from "built-in solvation" of the transition state by an adjacent "carboxyl-related" function.^{77b, 99} Aminations³⁶⁹ will be so affected by *carboxyl*, *carboxylate ion*, *carboalkoxy* and less so by carboxamido groups (cf. Section I, D, 2, b, structure **12**.) Other substitutions such as alkoxylation can be so affected by *carboxamido* and *amidino groups*³⁷⁰ (cf. Section I, D, 2, b, structure **14**). The effect of the cyclic hydrogen-bonded form (**63**) of 2-carboxamidopyridine on the reactivity of a leaving group is not known.

The effect of a *carboxy group* is illustrated by the reactivity of 2-bromopyridine-3- and 6-carboxylic acids (resonance and inductive activation, respectively) (cf. **166**) to aqueous acid under conditions which do not give hydroxy-debromination of 2-bromopyridine^{136a, b} and also by the hydroxy-dechlorination of 3-chloropyridine-4-carboxylic acid. The intervention of intermolecular bifunctional autocatalysis by the carboxy group (cf. **237**) is quite possible. In the amino-dechlorination (80°, 4 hr, petroleum ether) of 5-carbethoxy-4-chloropyrimidine³⁷¹ there is opportunity for "built-in solvation" (**167**) in addition to electronic activation. This effect of the *carboxylate ion*, *ester*, and *acid* and its variation with charge on the nucleophile are discussed in Sections I, D, 2, a, I, D, 2, b, and II, B, 1. A 5-*amidino group* activates 2-methylsulfonylpyridine toward methanolic ammonia.³⁷¹

A *cyano group* produces practical reactivity (methanolic CH_3O^- , 65°, < 3hr) by its presence in 2-chloro-3-cyano-6-methylpyridine,³⁷² opposing the deactivating effect of a methyl group, and on other 2-chloropyridines (see references 3-6 in ref. 140). The cyano group activates 3-cyano-5,6-diphenyl-2-methoxypyrazine³⁷³ (**168**) (pre-

pared in picoline from the 2-bromo analog and CuCN) sufficiently so that its isolation by acidification leads to hydrolysis of the methoxy group. The effect of a cyano group is also evident from the fact that the pyrazinone so produced is soluble in bicarbonate, like its 3-nitro analog and 2,4-dinitrophenol. The role played by the cyano group in 4-methoxylation³⁷⁴ of 3-chloro-4-cyano-5,6-dimethylpyridazine (**169**) with sodium methoxide is interesting. The chloro group (activated



by an *ortho* azine-nitrogen) can somewhat deactivate the cyano group by virtue of its electron-donating nature (*ortho* direct deactivation) relative to that of the cyano group (activated by a *para* azine-nitrogen) which is unable to exert a similar effect. On the contrary, the cyano group activates by stabilizing the charge in the transition state, and its activation produces reactivity considered similar to that expected of 3-chloro-5,6-dimethyl-*as*-triazine. Introduction of a 3-cyano group into 2-chloro-5-nitropyridine (cf. Table VII, p. 276) accelerates anilino-dechlorination 7,000-fold.

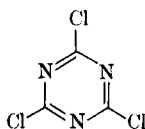
On 2-nitrochlorobenzenes (**164**), a 5-cyano group produces a 60-fold increase and a 4-cyano group a 6,000-fold increase in the rate of piperidino-dechlorination, primarily by lowering the energy of activation. A 4-carboxy substituent increases the rate 14-fold in spite of an unfavorable change in the entropy of activation, while a 5-carboxy group decelerates it 2-fold in spite of a favorable entropy change.³⁵⁸ Deactivation in the latter case is undoubtedly the result of greater anionization of the 5-carboxyl group (*para* to NO₂ and thus

more acidic); support for ionization affecting both is provided by the fact that a 4-carbethoxy group increases the rate 900-fold and a 5-carbethoxy group increases it 5-fold (both due entirely to lower energies of activation).

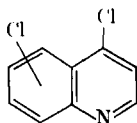
On benzenes,^{77b} the *amide group* is activating and, when in the *ortho*-position, gives an acceleration that has been attributed to its hydrogen-bonding (not given by an ester group) with the *extra* lone-pairs of the entering methoxide group (cf. 14). *Acetyl and benzoyl substituents*, like ester groups, give greater *para* than *ortho* activation.

b. *Halogeno, α,α -Dihaloalkyl, and Perhaloalkyl Substituents*. Activation by halogen groups in benzene derivatives³¹⁵ follows the order⁵⁴ⁱ *meta* > *ortho* > *para* and Br > Cl > I > H > F, although the latter series varies with the ring-position and the differences are sometimes not large.³⁵⁸ A *p*-trifluoromethyl group is more activating than a *m*- or *p*-halogen atom.³⁵⁸ In polyhalo-azines such as 2,4-dichloropyrimidine, the activating inductive effect of the chlorines on each other is approximately the same, but the mutual indirect deactivating effect of resonance is not equal (4 > 2). The net effect is that the 2-chloro group activates the 4-chloro more than the reverse. When a strongly electron-donating group like amino is inserted in any position, another unequal effect is introduced, and a reversal of reactivity (to 4 < 2) may result from the combination of the activating and deactivating factors. Various polyhalo heterocycles such as 2,6-dichloro-pyridine and -pyrazine, 2,5-dichloropyrazine, 3,6-dichloropyridazine, 4,6-dichloropyrimidine, 2,4,6-trichloro-*s*-triazine, and 2,6-dibromopyrazine^{375a} are especially reactive because of mutual activation by the halogens as well as a favorable statistical factor from the presence of several identical reactive sites. In the highly reactive 2,4,6-trichloro-*s*-triazine (170), the halogens are oriented for maximal mutual activation of each other, the ring-nitrogens are in the optimal 1,3,5-orientation, and the three-fold symmetry is statistically very favorable. An opposing, but obviously not predominating, effect of the chlorines is deactivating electron donation to the ring-nitrogens. In 2,4,6-trichloro-pyridine and -pyrimidine (cf. Table V, p. 274), the halogens are still ideally oriented, but the presence of fewer activating nitrogen atoms results in lower reactivity. In a *para*-substituted compound such as 3,6-dichloropyridazine, the additional halogen is activating relative to hydrogen and also reaction is statistically more favorable than in the monochloro analog. Although *para* halogens are less activating than *meta* halogens, they are still activating with

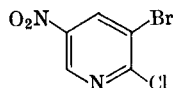
respect to hydrogen, with the possible exception of fluorine. Activation for nucleophilic substitution would be expected of $-\text{IO}$, $-\text{IO}_2$ and $-\text{}^+\text{IC}_6\text{H}_5$ substituents as a result of resonance stabilization of negative charge in the transition state, that for the latter involving d -orbital resonance. The $-\text{ClO}_3$ group in 4-perchlorylfluorobenzene is somewhat less activating for methoxy-defluorination^{375b} than a 4-nitro group.



[170]

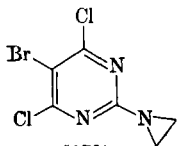


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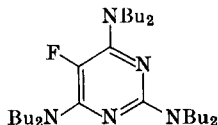


[172]

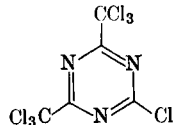
Several clear-cut examples of activation by a *halogeno substituent* are available. In kinetics studies,³⁶⁵ 6-, 7-, and 8-chloro groups on 4-chloroquinoline (**171**) produced 5–10-fold increases in the rate over that of the monochloro analog (cf. Tables X and XI, pp. 336 and 338, respectively). 3-Bromo-2-chloro-5-nitropyridine (**172**) is substantially more reactive toward potassium fluoride in dimethylformamide than is the des-bromo analog³⁷⁶; 2,6-dibromopyrazine is more reactive toward ammonia, alkoxide, hydroxide, and cuprous cyanide than are the 2,3- or 2,5-dibromo isomers.^{375a} The presence of a 5-bromo group enables 2,4-disubstitution of 5-bromo-4,6-dichloro-2-methylsulfonylpyrimidine by ethyleneimine in benzene at 40° (intermediate is **173**), whereas only 2-substitution of 4,6-dichloro-2-methylsulfonylpyrimidine occurs.³²⁵ The 5-chloro group in 2,4,5,6-tetrachloropyrimidine makes this compound more reactive (selectively at the 4-position)^{377, 378} than 2,4,6-trichloropyrimidine with amines and alkoxides. The often-presumed steric effect in such substitution is not great, and the normally less reactive 2-position is somewhat deactivated relative to the 4-position by the more effective *para*-quinoid electron-donating resonance of the 5-chloro substituent.



[173]



[174]



[175]

Tetraamination of 2,4,5,6-tetrafluoropyrimidine²⁷⁷ with dibutylamine involves the high reactivity of fluorine as a leaving group rather than activation by the 2,4,6-fluorines. The latter cannot account for the reactivity of the 5-fluorine since the 2,4,6-substituents undoubtedly all react first. Apparently, deactivation by the three dibutylamino groups so introduced (cf. 174) is diminished by steric hindrance to the necessary co-planarity with the ring.

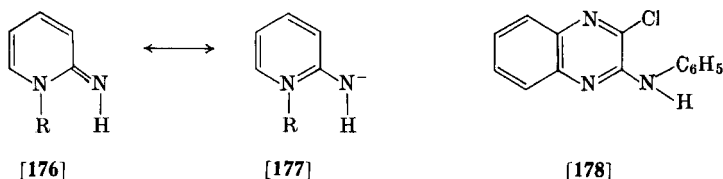
The activating effect of a *trichloromethyl* group is seen in the 2-dechlorination reactions of 2-chloro-4,6-bis(trichloromethyl)-s-triazine (175) with arylsulfonylhydrazides (24 hr) and heterocyclic amines (3 hr) at 20° and with unbasified primary and secondary alcohols (65°, 30 min). The 4,6-diphenyl or 4,6-bis(4-chlorophenyl) analogs do not react in this manner.²⁷¹

In piperidino-dechlorination of 2-nitrochlorobenzenes,³⁵⁸ the 500-fold acceleration by a 4-trifluoromethyl group (cf. 164) is greater than that by 4-chloro, -bromo, or -iodo substituents (6–12-fold), at least partly because deactivating electron-donating resonance is not as characteristic of perhaloalkyl groups; the 5-halo analogs show 25–35-fold acceleration. The acceleration by a 4-trifluoromethyl group is less than that by 4-carboethoxy (900-fold) and 4-cyano groups (6,000-fold)^{165,358} in 164. Relative rates of alkoxy-dechlorination of poly-(trifluoromethyl)-1-chlorobenzenes^{379a} are in the order: 2,4,6 > 2,4 > 2,6 > 2,5 > 4 > 2 > 3,5 \cong 3. The greater activation produced by a substituent when it is in the *para*-position than when it is in the *ortho*-position is clear from the 2,4 vs. 2,6 and 4 vs. 2 comparisons. On nitrohalobenzenes, trifluoromethyl groups are relatively inert to nucleophilic displacement⁷⁴ but they approach acetoxy and trimethylammonium groups in activating power.^{379b}

c. *Nitrogen*. The deactivating nitrogenous substituents are discussed first and then those that activate nucleophilic substitution.

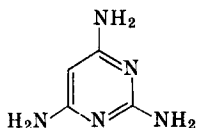
(1) *Deactivating amino substituents*. This category includes hydrazino, hydroxylamino, alkylamino, amino, ethyleneimino, arylamino, guanidino, ureido, anionic sulfonylamino, anionic nitroamino, azinone imino (176–177), acylamino, thioacylamino, and isothiocyanato groups (listed approximately in order of decreasing electron donation). Hydrazino and hydroxylamino groups are postulated to be more deactivating than an amino group in view of their having an adjacent lone-pair which contributes to the exceptionally high nucleophilicity^{125a} of hydrazine and hydroxylamine. The strongly basic amino (cf. 177) and guanidino groups will vary in effect depending on the

pH and on the extent of their protonation or hydrogen bonding to the solvent or reagent. The degree of anionization of nitroamino and sulfonylamino groups will alter their effect by increasing their electron-donating ability. The list begins with the strongest known non-ionic electron donors and proceeds to groups like isothiocyanato which could be somewhat activating. No work has been reported on the effect of an $-\text{N}(\text{CF}_3)_2$ substituent, but the deactivating effect of its amino-nitrogen should be overcome as it is in an acylamino substituent. The aminoalkylene group $(\text{R}_2\text{N}-\text{CH}=\text{CH}-)^{361c}$ is a vinylogous amino substituent and is deactivating.

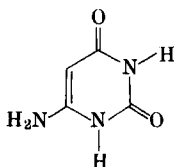


In aromatic amines, the nitrogen is nearly sp^2 -hybridized,³⁸⁰ permitting overlap of the amino lone-pair with the aromatic p -orbitals. From infrared frequencies, Mason^{381a} has calculated H—N—H bond angles and concluded that 2- and 4-aminopyrimidines have nearly trigonal amino-nitrogens with their lone-pairs in a $2p$ -orbital, which can conjugate completely with the heteroaromatic π -electrons. Further, 5-aminopyrimidine, like aniline, is more nearly tetrahedral with the lone-pair less effectively conjugating. Intramolecular hydrogen bonding between 2- or 4-amino groups and pyrimidine-nitrogens is weak, but not inconsiderable, in terms of orbital overlap; it is indicated by a doublet in the N—H stretching region^{381a} of the infrared spectrum of 4-methylaminopyrimidine.

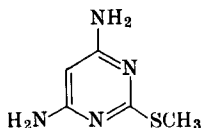
With certain nucleophiles (especially, but not only, with anilines as nucleophiles), the deactivation can be substantially overcome by acid catalysis.⁴⁷ Amino groups seem to be generally less deactivating than anionized hydroxy or oxo groups but are more deactivating than the unionized counterparts of the latter. Greater deactivation by an amino than by an unionized azinone oxo group was observed in the displacement of 2-methylthio or 4-amino groups from pyrimidines with amine acetates. Various amino derivatives such as **179** and **181** are unreactive²⁸⁰ while the corresponding pyrimidinones **180** and **182** react well.



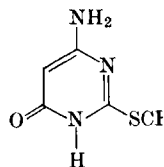
[179]



[180]



[181]



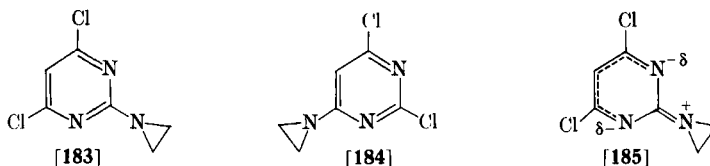
[182]

The deactivating effect of an amino group will of course decrease when it bears an electron-withdrawing moiety: $\text{NH}_2 \cong \text{NH}-\text{alkyl} \cong \text{N}-\text{dialkyl} > \text{NH}-\text{Ar} > \text{N}-\text{Ar}_2 > \text{NH}-\text{acyl} > \text{NH}-\text{sulfonyl} \cong \text{N}-\text{diacyl} > \text{N}-\text{disulfonyl}$. Greater deactivation from the *para*- than from the *ortho*-position is again the general rule. 4-Amino derivatives of pyridine, pyridazine, pyrimidine, quinoline, and quinazoline are 10–200 times more basic than their *ortho* amino analogs,^{355,356a} partly as a result of a similar electron donation. The *apparent* activating effect of introducing a 6-amino group into 5-bromouracil, in the reaction with alcoholic sodium disulfide,^{381b} is presumably due to its decreasing the deactivating anionization.

Deactivation in the order, dialkylamino $>$ alkylamino $>$ amino $>$ anilino, is indicated in several azines. This sequence is supported by a study³⁸² of the displacement of the chloro group from 6-anilino-2-chloro-4-(substituted amino)- and 6-anilino-2,4-dichloro-*s*-triazines with benzylamine or aniline. Second-order kinetics were observed, and the deactivating sequence, dialkylamino \cong alkylamino $>$ amino $>$ morpholino $>$ anilino $>$ alkoxy, is based on the relative rates (cf. Table VI, p. 275). 2,3-Dichloroquinoxaline with aniline under various conditions gives disubstitution via 2-anilino-3-chloroquinoxaline (178) (both direct and indirect deactivation) while alkylamines or ammonia give only mono substitution,³⁸³ thus indicating less deactivation by an *anilino group*. The indirect deactivation in 2-amino-6-bromopyridine vs. 2-dialkylamino-6-bromopyridine appears to be greater in the latter.³⁸⁴ The reverse was true in reaction of 4-substituted-2-nitrobromobenzenes (164) with piperidine.³⁸⁵ The rate of reaction²¹⁸ of 2-anilino-4,6-dichloro-*s*-triazine is about 140-fold less than that of the trichloro analog.

The deactivating effects of 2- and 4-amino groups in pyrimidine provide an interesting comparison. The 2-ethyleneimino group deactivates the 4- and 6-chlorines in 183 toward ethyleneimine in benzene at 50°, while the 4-ethyleneimino group in 184 deactivates the 6- but not the 2-chloro group.³²⁵ However, in contrast, 2-amino-

4-chloropyrimidine is reported to be more reactive³⁸⁶ to hot water or aqueous acid than is its 2-chloro-4-amino isomer; substitution occurs via acid catalysis in these reactions. In 2,6-dichloropyrimidines substituted at the 4-position with an electron donor, the 2-position is generally the more reactive (possibly involving hydrogen bonding to a ring-nitrogen by the reagent in some cases). The ground state resonance contribution by the *ortho*-quinoid structure **185** is presumably greater than the *para*-quinoid structure in the isomer because

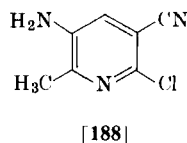
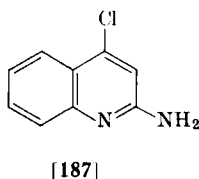
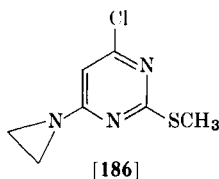


of its symmetry. Amination of 4-amino-2,6-dichloropyrimidine produced only 2-substitution, and 2-benzylamino-4,6-dichloropyrimidine could not be aminated.³⁸⁷ Methoxylation of 4-amino- or anionic 4-sulfanilamido-2,5- or 2,6-dichloropyrimidine produces only 2-substitution in contrast to reaction of 2,4,5- or 2,4,6-trichloropyrimidine with sulfanilamide anion at the 4-position.^{288b,388a-388c} Only one chloro group in 4,6-dichloro-2-methylthiopyrimidine, forming **186**, or its 5-bromo derivative reacts with excess ethyleneimine.³²⁵ The usually highly reactive methylsulfonyl group is unreactive in 4,6-diamino-2-methylsulfonylpyrimidine³⁸⁷ toward ammonia under various conditions.

Amination of 2,4,6-trichloropyrimidine in ethanol at 20° or 100° gives a mixture of the 2- and 4-amino products, both of which at 160° give 2,4-diamino-6-chloropyrimidine.³⁸⁹ The latter gives the triamine at 215°.³⁸⁹ The deactivated chloro group in 2,4-diamino-6-chloropyrimidine has reacted with alkoxides³⁹⁰ in alkanols at 120° for 6 hours or with benzylamine³⁹¹ in boiling butanol for 18 hours. 4-Amino-2,6-dichloropyrimidine undergoes disubstitution more readily with the more nucleophilic methoxide ion³⁹² than with ammonia. Combined deactivating effects exist in 2-amino-4-chloro-5-(*p*-chlorophenoxy)pyrimidine which can be aminated³⁹³ at 150° in ethanol (16 hr). Many additional examples of deactivation of different nucleophilic substitutions by various amino substituents are discussed in Brown's monograph on pyrimidines.³⁹⁴

The highly activated 2,4,6-trichloro-*s*-triazine with excess amines at

-15 to 0° gives mono-, at 20° di-, and at 130° tri-substitution.³⁹⁵ The conditions for complete substitution vary somewhat with the amine and with the solvent.³⁹⁶ The latter effect was noted in the progressively more difficult amination of tris(trichloromethyl)-*s*-triazine which goes to completion only in aprotic solvents.²⁷⁰ Tri-substitution (2 hr, 113°) of 2,4,6-trichloro-*s*-triazine with enamines or with heterocyclic methylene bases (aziniummethyl carbanions or zwitterions) is substantially more difficult than mono-substitution (30 min, 80°).^{361c}

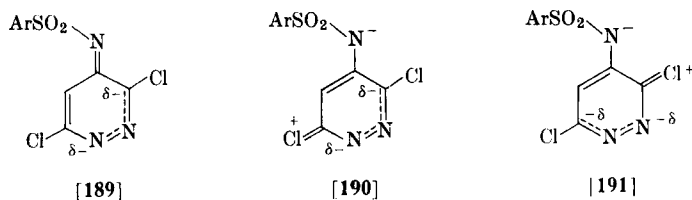


The indirect deactivation in 2-amino-4-chloroquinoline (**187**) requires vigorous conditions (potassium hydroxide in hot ethylene glycol, or boiling propanolic propoxide for 16 hr) to displace the chloro group, which is stable to aqueous alkali and to hydriodic acid.³⁹⁷ The direct deactivation in 5-amino-2-chloro-3-cyano-6-methylpyridine (**188**) prevents reaction with alkoxide ion under conditions which produce smooth reaction of the des-amino analog.¹⁴⁰

Both indirect and direct deactivation by an amino group are generally greater than by an alkoxy group. For example, reaction of 3-amino- and 3-methoxy-6-chloropyridazines with methoxide ion³²⁰ requires 20 hours at 120° and 8 hours at 65°, respectively. The greater deactivating effect of an anionic amino group³⁹⁸ is only partly compensated by an electron-attracting *N*-sulfonyl substituent in anionic 3-sulfanilamido-6-chloropyridazine³²⁰ and in anionic 4-sulfanilamido-6-chloropyrimidine^{263a} which is less reactive toward methoxide ion than is the 4-methoxy analog.

The selective reaction of anionic 3,6-dichloro-4-sulfanilamidopyridazine with excess methanolic methoxide at the 3-position^{360, 399a} is another indication of the absence of major steric effects in most nucleophilic substitutions, as a result of the direction of nucleophilic attack (cf. Section II, A, 1). The selectivity at the 3-position is an example of the interaction of substituent effects. The sulfonamide anion deactivates both the 3-chloro (*ortho* direct deactivation) and

6-chloro groups (*para* indirect deactivation) by electron donation (189) to the 3- and 1-positions. Both chlorines can donate electrons to the ring, but this action (190) from the 6-position is opposed by electron donation by the sulfonamide ion (189) to the same ring-positions; this opposition is not true for electron donation by the 3-chloro group (191). The reactivity of the 6-chloro group is therefore decreased by *para* indirect deactivation by the anionic sulfonamido group plus *para* direct deactivation by the 3-chloro group. 4-Amino-3,6-dichloropyridazine gives quantitative 3-substitution^{399b} with hydrazine hydrate in ethanol (78°, 3 hr) while the 4-amino-5,6-dichloro isomer is methoxylated (100°, 6 hr, 80% yield) at the 6-position. The apparent reversal of deactivating effect may involve hydrogen bonding to the ring-nitrogens.

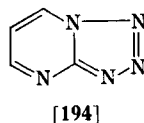
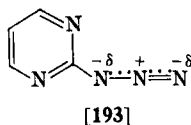
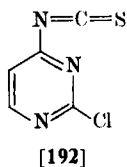


In piperidino-dechlorination of substituted 2-nitrochlorobenzenes,³⁵⁸ a 5-amino group produces only a negligible decrease in the rate, while a 4-amino group decelerates the reaction 1,000-fold.

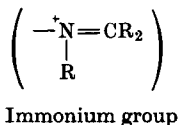
The deactivating effect of an *isothiocyanato* group is suggested by the failure of the 2-chloro group in 2-chloro-4-isothiocyanatopyrimidine (192) to react during its preparation from the 4-thiocyanato analog in boiling toluene or during subsequent mild reaction with ammonia or aniline to yield thioureido analogs.⁴⁰⁰ However, in its effect on the basicity of acridines, this group has a moderate electron-withdrawing effect ($\sigma_{m,p} + 0.33$)^{399c}; in the *ortho*- or *para*-position to a leaving group it can resonance-stabilize negative charge on its sulfur atom in the transition state for nucleophilic substitution.

The much greater ease of disubstitution^{21h,m} of 2,4-dichloropyrimidines with hydrazine (20°) than with ammonia (180°) is not a valid indication of less deactivation by the *hydrazino* group in the intermediate since hydrazine is a far better nucleophile than ammonia.^{125a} This difference is illustrated by the failure⁴⁰¹ to aminate 4-chloropyridazine-3,6-dione with ammonia at 160° overnight while it reacted with hydrazine at 20° in a few minutes (with heat evolution).

(2) *Activating nitrogenous substituents.* These groups are diazonium, nitro, nitroso, azoxy, azo, trimethylammonio, 1-pyridinium, sulfonylamino, nitroamino, cyanoamino, and azido, listed approximately in order of decreasing activation and electron-attracting ability. The latter group (cf. 193) has been little investigated, and the possibility



of ring closure to give a fused tetrazole (cf. 194), changing its effect, must be borne in mind. The trimethylammonio group exerts a strong inductive effect but cannot stabilize a negative charge by resonance. It is not as strongly activating in benzenes as the resonance activators —N_2^+ , —NO , —NO_2 , or $\text{—SO}_2\text{R}$ but activates more strongly than acetyl or trifluoromethyl groups.^{93, 402} The immonium group

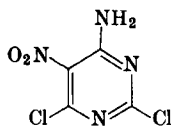


should facilitate nucleophilic substitution by induction even though it is electron-donating on demand of nitronium ion.^{399d}

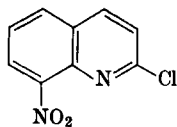
Chapman and co-workers^{167, 403, 404} have shown that, in the reactions of nitro-2-chloropyridines with piperidine, aryl amines, or pyridine bases, a 5-nitro group activates more than a 3-nitro group (cf. Table VII, p. 276).

The *nitro group* is usually more activating than a methylsulfonyl group, presumably due to better resonance stabilization of the negative charge on the substituent. The considerable activating effect of a 5-nitro group on various halopyrimidines has been well summarized by Brown.⁴⁰⁵ 2-Chloro-, 2,4-dichloro-, 4,6-dichloro-, and 4-amino-2,6-dichloro-pyrimidines are clearly more reactive toward amines or alkoxides when a 5-nitro group is present.^{406, 407} The 2,4-dichloro-5-nitro compound is aminated⁴⁰⁵ at the usually more reactive 4-position whose reactivity is probably also increased by an entropy

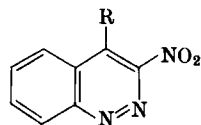
effect ("built-in solvation," discussed in Sections I,D,2,b and II,B,1,b). In marked contrast to 4-amino-2,6-dichloropyrimidine, which aminates "solely" at the 2-position, the 5-nitro derivative (**195**) aminates readily (cold ammonia), but only at the 4-position. In spite of a presumed steric factor, which would be increased in the 6-methyl analog, 2,4-dichloro-5-nitropyrimidine^{242,408} aminates "solely" and readily (ammonia, alkylamines, and anilines at 0°) at the 4-position, as does the 6-methyl derivative.⁴⁰⁹ In connection with the intervention of "built-in solvation," monoalkoxylation would be of interest but has not been reported.²¹⁰ The above mono-aminated pyrimidines react with the more nucleophilic methoxide



[195]



[196]



[197]

ion or methylamine under very mild conditions²⁴² as a result of the presence of the 5-nitro group. High reactivity relative to the des-nitro analogs is seen in amino-dechlorinations of 4-amino-2-chloro-, substituted 4-amino-2-chloro-, 6-amino-4-chloro-, and substituted 6-amino-4-chloro-5-nitropyrimidines^{21h,1} in which the deactivating effect of the amino group is largely overcome; in fact, it is usually necessary to use especially mild conditions to avoid diamination. Taylor and Thompson²⁴² found that acid-catalyzed amination produced an increased amount of 2-substitution: 3:1 ratio of 4- vs. 2-amino substitution of 2,4-dichloro-5-nitropyrimidine.

Only 4-amination of 2,4-dimercaptopyrimidine occurs with ammonia, methylamine, or dimethylamine, but both mercapto groups can be displaced in its 5-nitro derivative.⁴¹⁰

In 2-chloro-8-nitroquinoline (**196**), where resonance activation by the nitro group in the adjoining ring is possible, the chloro group is rapidly (10 min) displaced in boiling aqueous acid⁴¹¹ (cf. Table XI, p. 338).

The effect of other substituents and of the nucleophilic reagent on *ortho* vs. *para* reactivity in nitrobenzene derivatives has been discussed

by Bunnett.^{54h,77c} The accelerative effect of a 5-nitro substituent on the reactivity of 2-methylsulfonylpyridine³¹⁷ and on 2-chloro-3-cyano-6-methylpyridine and other 2-chloropyridines¹⁴⁰ with various nucleophiles has been reported. Activation by the nitro groups has been observed in the following displacements: of the chloro group in 3-nitro- and 3,5-dinitro-4-chloropyridines and in 2-chloro-3,5-dinitropyridine by water or ethanol; of the 4-substituent in 3-nitro- and 3,5-dinitro-4-aminopyridine by alkali and in 4-methoxy-3-nitropyridine by *n*-propylamine; and of the sulfonate group in 5-nitropyridine-2-sulfonate salts by several reagents.⁴¹² 2-Chloropyridine is activated by a 5-nitro substituent toward hydrazine (20°), hydroxide (100°), or hydrosulfide (50°).^{129a} 3-Nitro- and 5-nitro-2-chloropyridines undergo satisfactory fluoro-dechlorination with potassium fluoride in dimethylformamide, the 5-nitro being considerably more reactive, while 2-chloropyridine itself and its *N*-oxide do not react.³⁷⁶

The 4-substituents in 4-amino- and 4-chloro-3-nitrocinnolines (197) are readily displaced at 95° with dilute aqueous alkali or with aniline, respectively.⁴¹³

The comparison of effects of a nitro group and an azine-nitrogen (pyridine and pyrimidine) made by Mangini and Frenguelli⁴¹⁴ and by Chapman *et al.*^{55, 167} lead to the conclusion that the nitro group is the more activating. However, the comparison is not simple theoretically and will vary with the reagent and the reaction conditions. The relative reactivities with ethoxide ion are 900:180:90:2 for 4- and 2-chloronitrobenzene and 4- and 2-chloropyridine, respectively. Theoretical comments on the large difference in the *ortho*:*para* ratios in these four compounds have been made recently.¹⁵ An alternative explanation is that greater dispersal of the negative charge in space contributes to the reactivity of the *ortho*-nitro compound being so much higher than that of the *ortho*-aza analog, relative to the reactivities of the *para* analogs. The relation of the reactivity of 2,4-dinitrochlorobenzene and 2- and 4-chloropyrimidines with alkylamines, aniline, or pyridine has also been studied by Chapman and Rees.¹⁶⁷ A 4-nitro substituent on 2-nitrochlorobenzene produces a 40,000-fold increase in the rate of reaction (entirely by decreasing the energy of activation) with piperidine in benzene.³⁵⁸

The effect of a *nitroso group* on the alkaline deamination of 4-nitroso-*N,N*-dialkylanilines has been studied kinetically and the mechanism discussed.^{420a} A 5-nitroso substituent on 4-amino-6-hydroxy-2-

methylmercaptopyrimidine activates the 2-methylmercapto group for substitution (20°, 90 min, 70–90% yield) with various amines more than a 5-nitro group does.^{420b}

The activating effect of the *phenylazo* group in the reaction of 6-chloro-5-phenylazo-2,4-diaminopyrimidine and its analogs with amines or with dimethylformamide has been noted by Brown.²¹¹ The activating effect in 4-nitroso-, 4-phenylazoxy-, and 4-phenylazo-2-nitrochlorobenzenes has been studied kinetically.^{93, 415}

The relatively infrequent availability of stable *heterocyclic diazonium* compounds explains the paucity of information on this group. In diazotizing 5-amino-2,4-dichloropyrimidine,⁴¹⁶ the chlorines are displaced by hydroxy groups. A related type of activation is also indicated by the very ready decarboxylation of 5-aminopyrimidine-2,4-dione-6-carboxylic acid upon diazotization.⁴¹⁷ In diazotizing and deaminating 8-amino-5,7-dibromoquinoline in hydrochloric acid, 5,7-dichloroquinoline was chiefly formed.⁴¹⁸ 4-Substitution of 4-chloro-, 2,4-dichloro-, and 2,4,6-trichloro-benzenediazonium salts with trimethylamine in acetonitrile occurs instantaneously at –18° in very high yield.¹⁰⁰ The striking activation or *ortho* or *para* substituents in benzenediazonium compounds toward weak nucleophiles has been observed, e.g., the *self-diazotization* of 2,5-dinitroaniline by means of hydrochloric acid in acetic acid to yield 2-chloro-5-nitrobenzene diazonium ion [see references 47 and 48 in reference 77(c)]. In substituted nitrohalobenzenes, the diazonium group is more activating than nitro and trimethylammonio groups.^{415, 419}

A *1-pyridinium* substituent has an activating effect on nucleophilic substitution of pyrazines³⁰² and *s*-triazines.^{361c}

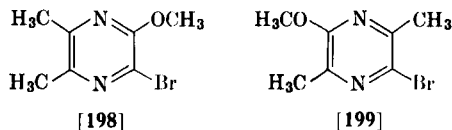
d. *N-Oxides and Their Derivatives*. The activating effect of these substituents and of other forms of cationization of azine-nitrogen is discussed in Section II, C.

e. *Oxygen*. Groups linked to the ring by an oxygen atom include anionic hydroxy, aminooxy, alkoxy, unionized hydroxy, aryloxy, acyloxy, oxo, cyanato, and sulfonyloxy, listed approximately in order of decreasing deactivation. Three forms of “hydroxy” must be considered: anionic hydroxy (same as anionic oxo), true heteroaromatic hydroxy (usually, but not always, *beta* or *meta* to a ring-nitrogen), and oxo [“hydroxys” *alpha* (*ortho*) or *gamma* (*para*) to a ring-nitrogen generally assume this form^{331a} unless prevented from doing so by some structural feature, e.g., 6-hydroxy-4-pyrimidinone or 3-hydroxy-6-pyridazinone]. Aryloxy seems to be only slightly

deactivating, and those below it in the list are activating. Perfluoroalkoxy groups such as $-\text{OCF}_3$ should be activating, based on ionization constants of substituted anilines, phenols, and benzoic acids.^{421a}

(1) *Alkoxy, aryloxy, and acyloxy*. The alkoxy group is considered as deactivating when it is *meta* as well as when it is *ortho* or *para* to the leaving group since indirect deactivation via electron donation to an activating azine-nitrogen generally is possible. However, indirect deactivation in benzenes is not always discernible, e.g., in piperidino-dechlorination³⁵⁸ of substituted 2-nitrochlorobenzenes, a 5-methoxy or 5-ethoxy group produces a 4-fold *increase* in rate (due to a lower activation energy) relative to a 5-hydrogen. In other instances, the rate may be either unaffected or lowered, as in the 3-fold deceleration of methoxy-dechlorination of 5-methoxy-2,4-dinitrochlorobenzene.^{421b} Direct deactivation by a 4-methoxy or 4-ethoxy group is clearly seen in a 40-fold decrease in the rate (due primarily to increased energy of activation) of piperidino-dechlorination³⁵⁸ of 2-nitrochlorobenzene.

A comparison of *ortho* vs. *para* direct deactivation by a methoxy group has been made by Karmas and Spoerri^{223b, 373} in 2,3-dibromo-5,6-dimethyl- and 2,5-dibromo-3,6-dimethyl-pyrazine. The former gives monomethoxy-debromination with one equivalent of methanolic methoxide (65°, 6 hr) and disubstitution via **198** with excess reagent for a longer time (10 hr). In contrast, the isomeric 2,5-dibromo compound gave only monosubstitution, forming **199**, under the latter conditions.



Disubstitution in the related 2,5-dichloro-3-phenylpyrazine⁴²² required much more vigorous conditions (120°, 15 hr) than monosubstitution (65°, 2 hr). With 2,5-dichloro-3,6-dimethylpyrazine monomethoxylation occurred in high yield at 78° (8 hr), but, again, disubstitution required a higher temperature (120°, 8 hr). In contrast, 2,6-dibromopyrazine disubstitutes with methoxide ion more readily,^{375a} the indirect deactivation being less effective than the direct deactivation above (cf. **198**). A comparison of *ortho* vs. *para* direct deactivation in 2-amino-3,5-dibromopyrazine shows that the *para* direct deactivation is the more significant in controlling the site of reaction with a variety of nucleophiles: hydroxide, methoxide, or hydrosulfide

ions, dimethylamine, piperidine, or ammonia. 3-Substitution products were isolated in 60–70% yields.^{357b}

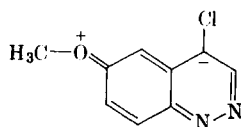
Direct deactivation by a methoxy group makes 3-chloro-6-methoxypyridazine unreactive^{254, 320} toward sulfanilamide anion in contrast to its 6-chloro, 6-methyl, and 6-hydrogen analogs. Both direct and indirect deactivation of the two chlorines in 3,6-dichloro-4-methoxypyridazine (**160**) are possible; the greater reactivity^{320, 361a, 362} at the 3-position suggests that *para* indirect is stronger than *ortho* direct deactivation by the methoxy group. However, the steric effect of solvation by hydrogen bonding (**162**) at the more electron-rich 1-position appears to be important (cf. effect in the 4-methyl analog, Section II, E, 2, a).

The decreased reactivity of 4-chloropyrimidines bearing 6-methoxy^{263a} or 2,6-dimethoxy^{263a, 289a} substituents has been noted especially with relatively poor nucleophiles such as the sulfanilamide anion. The progressive substitution of 2,4,6-trichloropyrimidine^{21j, n} with methanolic methoxide proceeds first at 0° (4-position), then at 20° (2-position), and the final substitution occurs at 70–100°; 2-amination of 2,4-dichloro-6-methoxypyrimidine proceeds at 100°. Successive methoxy-debrominations of 2,4,6-tribromopyridine require higher temperatures¹⁸³ for each additional step. The methoxy groups must be exerting an indirect resonance-deactivation. A similar effect was observed in mono-, di-, and tri-methoxylations of 2,4,6-trichloro-*s*-triazine, which require progressively higher temperatures⁴²³; deactivation by the group introduced into the same substrate was in the order $\text{NH}_2 > \text{ArNH} > \text{EtO} > \text{MeO} > \text{ArO}$ (cf. Table VI, p. 275). The same effect was observed in triethoxylation of 2,4,6-tris(trichloromethyl)-*s*-triazine⁴²⁴ and in poly-methoxylations and -phenoxylation of 2,4,6-tribromopyridine¹⁸² and of 3,6-dichloropyridazine.^{320, 425}

Indirect deactivation by an alkoxy group is apparent in the sluggish reaction of 4-butoxy-2-chloroquinoline with *n*-butylamine⁴²⁶ (EtOH, 5 hr, 180°, but not at 80°). The chloro group in 2-chloro-4-ethoxyquinoline is more reactive⁴²⁷ than that in the 4-chloro-2-ethoxy isomer toward alkoxides or amines in spite of the usually more effective *para* indirect deactivation in the former. For kinetic data on quinolines see Tables X and XI, pp. 336 and 338, respectively.

Direct deactivation transmitted from the adjoining ring (cf. **200**) is appreciable in making 4-chloro-6-methoxycinnoline less reactive^{283b} than the 6-H analog toward phenoxide ion (cf. Tables X and XI).

Little evidence is available on activation by acyloxy groups. Carboxylic reagents form stable *N*-acylazinones, probably via rearrangement of unstable *ortho*- or *para*-acyloxyazines. These and *meta*-acyloxy derivatives are likely to be unstable toward many nucleophiles. In nucleophilic substitution^{379b} of nitrohalobenzenes, an acetoxy group has an activating power similar to CF_3 and Me_3N^+ . The effect of inorganic acyloxy is not clear-cut since reactions of such derivatives are usually complicated by acid catalysis, e.g., **201** where Z is SOCl or POCl_2 and Le is NO_2 or halo.^{223b, 298}

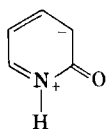


[200]

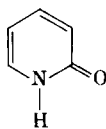


[201]

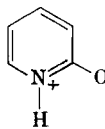
(2) *Hydroxy and oxo*. Substituents on any position of so-called hydroxyazines or azinones are often regarded as not prone to nucleophilic displacement since electron-donation (cf. **202**) to the ring-positions *ortho* or *para* to the oxygen clearly occurs on demand of electrophilic reagents which thereby readily substitute (positions *ortho* to the oxo group are favored), and halogen groups so introduced are often, but not always, unreactive. However, various data indicate that electron-withdrawal from the ring-positions *meta* to the oxo group exists in the ground state and that such compounds are aromatic as a consequence of the resonance shown in structures **202–205**.



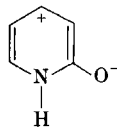
[202]



[203]



[204]



[205]

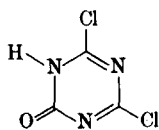
Nuclear magnetic resonance measurements have led to the conclusion²²⁴ that 2-pyridones have about 35% of the aromaticity of *benzene* and that the formally related 1,2-dihydro-2-methylenepyridine is not aromatic. A substantial contribution by such resonance is indicated by the electronic spectrum of 2-quinolone, which is

essentially the same^{11c} as that of 2-naphthol, and by that of 6-hydroxy-2-methylpyridazin-3-one^{428a}. The 2-pyridone moiety is electron-attracting²²⁵ in the ground state, as demonstrated by the acid-strengthening effect observed in the ionization equilibria of 5-hydroxy- and 5-carboxy-pyridines on insertion of a 2-oxo group. This effect is opposite to that observed in 2-aminopyridines, which generally do not exist in the analogous imino form.^{331b} X-ray crystallographic data on 2-pyridone have been considered evidence that the zwitterionic resonance forms make a large contribution (ca. 50%) to the structure of the resonance hybrid.^{428b}

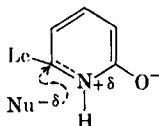
The oxo group will tend to activate nucleophilic substitution when its oxygen atom is protonated (e.g., **201** when Z is H) in acid-catalyzed reactions^{223b, 298} or by hydrogen bonding to the solvent. Acceleration due to a favorable increase in the entropy of activation can arise from hydrogen bonding of the nucleophile or its conjugate acid to the oxo oxygen atom. Deactivation will, of course, result when the azinone is anionized. For example, 2,4,6-trichloro-*s*-triazine with alkali at low temperatures gives 2,4-dichloro-*s*-triazin-6-one anion (**206**) and at room temperature gives 2-chloro-*s*-triazine-4,6-dione anion.^{428c} The chloro group in this anion is stable to aqueous hydroxide but not to the more nucleophilic methoxide ion; when not anionized, it is displaced readily by acidic water or by aniline (the latter reaction is autocatalytic). The presence of a good leaving group or electrophilic substituent in an azinone makes the NH group more acidic and, consequently, strongly basic nucleophiles produce complete anionization and little displacement. However, when an azinone ring-nitrogen is alkylated or arylated, anionization cannot occur and such derivatives react quite readily even with strongly basic reagents (*vide infra*).

Reactivity in azinones seems best approached on the basis of activation *ortho* and *para* to the ring-nitrogen, considered as partly cationic (cf. **202** and **204**), and potential deactivation *ortho* and *para* to the oxygen (or *meta* to the ring-nitrogen). The comparable reactivity of 2-bromo-6-pyridone and 2-bromopyridine^{129a} seems more realistically viewed as arising from the resonance contribution of **204** than from the reactions of the former being of a "non-aromatic" type. There seems to be weak deactivation, if any, when azinones are not anionized. There are several examples of greater reactivity of substituents which are *ortho* or *para* to increasing numbers of azinone-nitrogens. Some examples of the reactivity of leaving groups adjacent

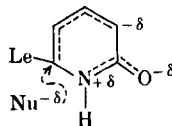
to the oxo substituent can be rationalized as due to hydrogen bonding of the reagent to the partly anionic oxo oxygen. A true hydroxy group, such as in 3-hydroxypyridine,^{331a} can exert a deactivating effect both in its Azine—OH and Azine—O⁻ forms.



[206]

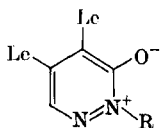


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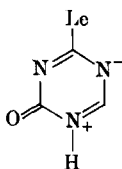


[208]

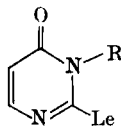
Nucleophilic substitution can be facilitated *ortho* and *para* to the partly cationized ring-nitrogen (see discussion of cationization in Section II, C) with an electrostatic factor tending to favor reaction at the *ortho*-position. The negative charge donated by the nucleophile can be stabilized in only three monoanionic resonance structures, as with the non-oxygenated analog, but the presence of the oxygen permits distribution of the charge over a greater space (cf. 207) and the charge on the ring-carbons is stabilized by two possible partly tri-ionic structures (208). Nucleophilic substitution at the 3-position of 2-pyridone involves activating, inductive stabilization of the charge



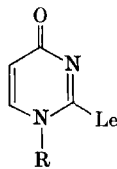
[209]



[210]



[211]

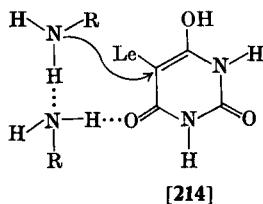
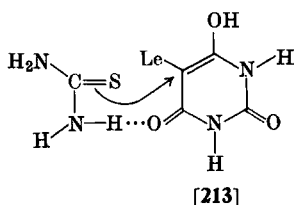


[212]

at the 6-position opposed by deactivating, electrostatic repulsion of the nucleophile by the partial negative charge at the 2-position (cf. 204 and 205), plus conjugative electron donation (cf. 202) from the partly anionic oxygen. A comparison of the relative influences of these effects can be made in various 4,6-, 5,6-, or 4,5-dihalo-2-pyridones (209, R = H) or in their N²-substituted analogs, some of which are discussed below. In the 4,6-dihalo compounds, the more reactive 4-halo group is resonance-activated by a *para* ring-nitrogen and deactivated by conjugation with a partially negative oxygen at

the *ortho*-(3-)position, while the 6-halo group is activated by an *ortho* ring-nitrogen (generally less effectively) and deactivated (more effectively) by conjugative electron donation from the *para*-(3-)position. Both halogeno groups are activated nearly equally by induction ($=+NR-$ in the 2-position). In **209**, the less reactive 4-halogen is deactivated by conjugation with the oxygen and, although both halogens are resonance activated by *para* nitrogen atoms, the one activating the 5-halogen is partly cationized. This cationic difference between the two ring-nitrogens is less significant in the concurrent inductive activation by the other nitrogen atom. The net effect in 3-pyridazinones is 5- > 4- > 6-position in reactivity. The relation of electron donation to electron attraction may be different in *s*-triazine compared to pyridine as a result of the contribution of resonance structures such as **210** but kinetic data are not available. In the 2-substituted pyrimidin-4-ones **211** and **212** and their 6-substituted analogs, different degrees of reactivity are possible depending on where the *N*-substituent or hydrogen^{331a} is located.

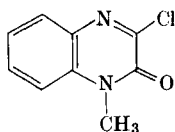
A bifunctional autocatalytic effect of azinones in general is possible in certain nucleophilic reactions such as amination. Zollinger²¹⁸ has found that 2-pyridone is the best catalyst for anilino-dechlorination of various chloroazines. It seems likely that examples of autocatalysis will be found when the substrate contains an azinone moiety. The azinone *by-products* of displacement reactions may also function in this way⁴⁷ as catalysts for the main reaction.



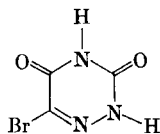
Several examples have been reported of the progressively greater reactivity of a 5-pyrimidinyl halogen the more oxo groups that are present, an effect not produced by more amino groups. Bonding of the reagent (cf. **213** or **214**) can produce a favorable entropy of activation change with or without a cyclic transition state. Another view would be to regard the displacements as aliphatic S_N2 in nature with a type of bromomalondiamide substrate or, when the substrate is anionized, as S_N1 as occurs in some halomalonate ions.^{429a}

Occasionally, displacements^{223b,298} occur in the process of reacting oxoazines with phosphorous oxychloride or pentasulfide or with an arylsulfonyl halide, thionyl chloride, or sulfuryl halide. The phosphoryloxy or sulfonyloxy intermediates (**201**) are now activated by virtue of the protonated ring-nitrogen plus the electron-attracting acyloxy substituent.

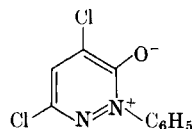
3-Chloro-1-methyl-2-quinoxalinone (**215**), which cannot anionize, reacts readily^{429b} with *N*-methylaniline. 6-Bromo-*as*-triazine-3,5-dione (**216**) is largely anionized by dimethylamine but not by thiourea



[215]



[216]



[217]

under the reaction conditions.^{430a} The acid hydrolysis (boiling 6*N* sulfuric acid, 16 hr) of 2,5-dichloro-3,6-dimethylpyrazine⁴²² seems to stop at mono-displacement as does that of 3,6-dichloropyridazine, thus indicating some deactivation (relative to the effect of a chloro group). Anionized 3-chloro-6-pyridazinone is relatively unreactive to hydroxide or alkoxide ions but reacts well⁴²⁵ with the more nucleophilic hydrosulfide ion. The deactivating effect of anionization does not prevent displacement of a good leaving group. For example, 5,6-diphenyl-2-nitro-3-pyrazinone in pyridine forms the 2-pyridinium derivative in spite of its anionization while the 2-chloro analog does not.²⁹⁸ The latter reacts with pyridine under acid catalysis, however.

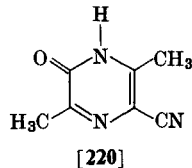
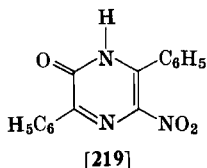
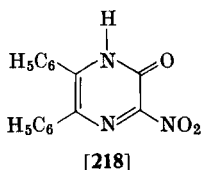
An orientation of leaving group to azinone moiety suitable for activation or, at least, appreciable reactivity exists in various 3-pyridazinones. 6-Bromo- and 6-chloro-2-phenyl-3-pyridazinones react at 20° with methylamine.^{430b} In 4,6-dichloro-2-phenyl-3-pyridazinone,^{430b} inductive *meta* activation by the partly cationic ring-nitrogen (**217**) is similar for both halogens, but the reactive 4-chloro group is activated by a *para* ring-nitrogen while the unreactive 6-chloro group is activated by an *ortho* ring-nitrogen, with the reverse relation for any deactivation by the partly anionic oxygen atom. The greater *para* activation and *para* deactivation act in concert to favor 4-substitution. A 4-chloro group on 6-methyl-2-phenyl-3-pyridazinone

is relatively reactive toward ammonia and amines^{431a, 431b, 432a} or toward ethoxide ion.^{432b, 433a}

The different activation and deactivation influences are seen in 4,5-bromo-2-phenylpyridazin-3-one (**209**) which reacts^{433b, 434a, 434c} with methoxide, hydrazine, or secondary amines at the 5-position. Related N—H and *N*-alkyl halopyridazinones behave similarly.^{434b}

Of comparable origin is the reactivity^{435a, 435b} of 5-chloro-2,6-dimethyl- and 5-chloro-1,6-dialkyl-pyridazin-3-ones with ammonia, amines, alkoxides, and cyanide ion. The exact relation of the reactivity of these azinones to the corresponding parent compound is not clear without a direct qualitative comparison or kinetic data.

Greater *para* than *ortho* deactivation is seen in the hydrolysis (HCl in AcOH, 100°, 1 hr) of the nitro group in 5,6-diphenyl-2-nitro-3-pyrazinone (**218**) but not in 6-phenyl- or 3,6-diphenyl-2-nitro-5-pyrazinone (**219**).^{223b} Similarly, acid hydrolysis of a 2-bromo substituent in 3-pyrazinone, but not in 5-pyrazinone, is readily accomplished. All five of these pyrazinones are stable in strong alkali or alkoxide as a result of complete anionization. Decreased reactivity of



anionic azinones is shown by the decreased reactivity, relative to 4-chloropyrimidine, of 2-alkyl-4-halo-6-pyrimidones with aqueous ammonia (100°) or of 4-chloropyrimidine-2,6-dione with methylamine (130°).^{21j} 2,5-Dicyano-3,6-dimethylpyrazine with 1*N* alkali (20°, 4 hr) readily forms the anion of the mono-oxo analog²⁶⁷ (**220**); more drastic conditions cause hydrolysis of the remaining cyano group (to the carboxy group) rather than displacement.

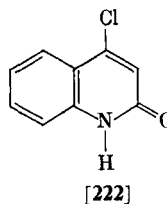
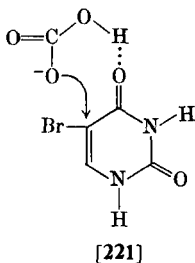
Certain oxypyrimidines react almost as readily as non-oxygenated compounds. Thus, 6-chloro-1,3-dimethylpyrimidine-2,4-dione and its 5-methyl derivative react with ammonia and primary or secondary amines at 20° or on very brief warming.^{226, 436a}

The oxo group facilitates reaction relative to H, CH₃, or NH₂ substituents on pyrimidines in the displacement of mercapto, arylthio, or amino groups by amines. The 2-thioxo group is reactive toward

amines³²⁹ in 2-thiobarbituric acid but not in 2-thioxo-4-oxo-, 2,6-dithioxo-, 2-thioxo-4-amino- (or substituted 4-amino-)pyrimidines. The more reactive 2-alkylmercapto group seems to react better in the presence of oxo groups, e.g., in the *S*-methyl derivatives of 2-thiobarbituric acid or 2-thiouracil.^{436b} In 6-methyl-2-methylthio-4-substituted-pyrimidines, reactivity toward aniline or 2-diethyl-aminoethylamine is greater when the 4-substituent is an oxo group than when it is a methyl group.^{437a, 437b, 438a} Many of these aminations are facilitated by acid catalysis, often of the bifunctional type. Methylamine acetate aminates 2-methylthiopyrimidines when the latter compounds are substituted with 4-oxo or 4-oxo-6-amino groups (182) but not with 4-amino or 4,6-diamino groups (181); 4-aminopyrimidines transaminate when substituted with 6-oxo-2-amino or 2,4-dioxo groups (180) but not with 2,6-diamino groups (179).²⁸⁰ 4,6-Dichloro-2-pyrimidone reacts readily with thiourea.³²⁵

The high reactivity of 5-halopyrimidines bearing oxo groups may be due to hydrogen bonding of the reagent to oxo groups (213 and 214) or to a change in mechanism.^{429a} 5-Bromobarbituric acid and its 6-amino analog, but not 5-bromouracil, react at room temperature with alcoholic thiourea^{438b}; the reactivity of 4-amino-5-bromopyrimidin-6-one is puzzling. Their *N*-alkyl analogs^{439b} are no more reactive since anionization under the reaction conditions is slight. Similar reaction^{439b} occurs rapidly at 78° with 2,4-diamino-5-bromopyrimidin-6-one, which also reacts with morpholine and 2-thiobenzoic acid. 5-Bromo-4-hydroxypyrimidin-6-one is reactive toward aqueous thiourea (100°) while 5-bromo derivatives of 6-pyrimidinone and 4,6-dimethoxy- and 4,6-diamino-pyrimidine do not react.^{440a} Alcoholic amines at 70–80° rapidly aminate 6-amino-5-bromo-1,3-dimethylpyrimidine-2,4-dione.^{440b, 441a} The reasonably good reactivity of 5-chloro-4-hydroxy-2-hydroxymethylpyrimidin-6-one^{441b} (complete in 12 hr at 78°) with excess ethanolic ethoxide is possibly due to the deactivating effect of the anionic oxygen atoms being overcome by their hydrogen bonding solvation [cf. 214] by the conjugate acid of the nucleophile plus the resulting favorable proximity of the reagent to the 5-position. A related effect may be operating in the amination^{442a, 442b, 443a} of 5-bromouracil. Hydroxy-debromination of 5-bromouracil requires vigorous conditions when it is completely anionized by strong alkali, but milder conditions^{443b} suffice with boiling sodium bicarbonate since there is less ionization of the azinone. A bifunctional catalytic effect (cf. 221) of bicarbonate is possible under

the latter conditions. 5-Bromo-2-oxo (or amino or substituted amino)-4-pyrimidinones are readily substituted (78° , 4 hr, 20–90% yields) at the 5-position with substituted *o*-aminothiophenoxide ions; a 6-oxo substituent facilitates the reaction.^{442c} In the subsequent acid-catalyzed ring-closure of the 5-(*o*-aminophenylthio)-4-pyrimidinones, nucleophilic displacement of the 4-oxo group by the anilino moiety occurs.



Deactivation in the anion formed under the reaction conditions prevents alkoxy-dechlorination of 4-chloro-2-quinolone (**222**) with boiling alkoxide solution while 4-chloroquinoline and its 2-ethoxy and 2-anilino derivatives react.^{443c, 443d} 4-Chloro-*N*-methyl-2-quinolone reacts readily.

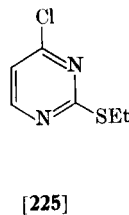
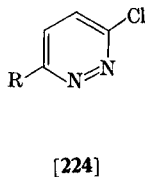
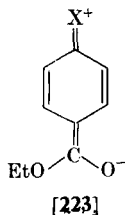
f. *Sulfur*. Groups linked to azines through sulfur include dialkylsulfonio, arylsulfonyl, alkylsulfonyl, sulfonic acid and ester, sulfamoyl, aryl- and alkyl-sulfinyl, sulfinic acid, thiocyanato, acylthio, ring thioxo (ring C=S, often named as mercapto), arylthio, anionic sulfamoyl, sulfonate anion, true unionized mercapto (—SH), alkylthio, and anionic thioxo or mercapto, arranged approximately in the estimated order of decreasing activation. The last group is presumably less deactivating than an anionic oxo or hydroxy group. Azine “mercapto” groups *ortho* or *para* to a ring-nitrogen generally exist in the thioxo form.^{331a} Azinethiones will be more anionized than the less acidic oxygen analogs under the same conditions, so comparison of their reactivity must take this into account. In general, the alkyl-, aryl-, and acyl-thio substituents are much less electron-donating than the oxygen analogs and can, on demand, appreciably stabilize a negative charge by resonance involving expansion of the sulfur outer shell to 10 electrons. Thus, a methylene carbanion is stabilized by an adjacent alkylthio group^{443e} but not by an alkoxy group. Nucleophilic additions to alkylthioacetylenes occur more readily than to alkoxyacetylenes; the nucleophile adds to the more electron-deficient

terminal acetylenic carbon in the former and to the adjacent carbon in the latter.^{444a, 444b} Resonance involving expansion of the sulfur outer shell to 10 or 12 electrons in arylsulfones and arylsulfonamides seems established,^{315, 444c, 445a} and stabilization of the negative charge can thereby be accomplished. The stability of hydrogen bonds formed by sulfur groups with the solvent is generally considered to be less than those formed by the corresponding oxygen compounds, but hydrogen bonds to thioxo groups have considerable strength.^{445b} It seems likely that cyclic transition states having the nucleophile (or its conjugate acid) hydrogen-bonded to an adjacent thioxo group (cf. **213** and **214**) will be stabilized about as well as those involving an oxo group.

The new aromatic substituents $-\text{SF}_5$, $-\text{SCF}_3$, and $-\text{SO}_2\text{CF}_3$ all have an increased electron-withdrawing effect relative to their non-fluorinated analogs, based on ionization constants of substituted anilines, phenols, and benzoic acids as well as on reduction potentials of substituted nitrobenzenes.^{421a, 421c} The $-\text{SF}_5$ group approaches a nitro group in electron attraction and a $-\text{SCF}_3$ substituent has a somewhat greater effect than an acetylthio group. The $-\text{SO}_2\text{CF}_3$ group is second only to the diazonium group in electron withdrawal as measured by the methods above. In nucleophilic transalkoxylation^{421d} of 4-substituted 2-nitroanisoles the $-\text{SO}_2\text{CF}_3$ group was by far the most reactive (20°, 30 min) in the series $\text{SO}_2\text{CF}_3 > \text{NO}_2 > \text{SO}_2\text{CH}_3 > \text{CF}_3$, the latter reacting in 30 min at 70°.

The *alkylthio* group is the most investigated sulfur-containing substituent. On the basis of its sigma constant^{268a} it is a very weak electron donor, but in 4-methylthio-2-nitrochlorobenzene it is activating by 20-fold,³¹⁵ with respect to the 4-H analog (cf. Table XI, p. 338, for activation in quinolines). The higher reactivity of the halogen in alkylthio-azines compared to that in alkoxy-azines arises mainly from failure of the alkylthio group to deactivate by donating electrons, the inductive charge stabilization in the transition states being similar. The contribution of the substituent X to the resonance energy of **223** has been estimated^{446a}: when X is dimethylamino and amino it is about 0.9 kcal, for methoxy 0.45 kcal, and for methylthio and fluorine about 0.2 kcal, all relative to hydrogen (0 kcal). In contrast to the sulfur 3*p*-orbitals, the 2*p*-orbitals of oxygen cannot effectively form π -bonds^{2d} with π -electron systems such as those of an azine-ring and thereby donate electrons to the ring. The resulting difference in the deactivating effect was noted in relation to the lower

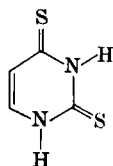
reactivity of 4,6-dimethoxypyrimidine vs. 4,6-bis(methylthio)pyrimidine toward sulfanilamide anion.²⁶⁴ Further, 3-chloro-6-methylthiopyridazine (**224**, R = MeS) is much more reactive toward sulfanilamide anion than are the 6-methyl and 6-methoxy analogs, the latter being much less reactive even under more vigorous conditions.²⁵⁴



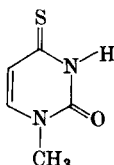
These pyridazines are subject to direct deactivation of the leaving group. It would appear from the conditions used in its reactions with ammonia (115°)^{446b} and methylamine (50°)⁴⁴⁷ that 4-chloro-2-ethylthiopyrimidine (**225**) is somewhat deactivated (indirect). In various aminations of pyrimidines, the effect of an alkylthio group seems to be very mildly deactivating,^{21g,k} like that of methyl groups. However, these surmises from the conditions used are not as reliable as the direct qualitative comparison described above and the kinetic data.³¹⁵

The effect of the *thioxo moiety*, like that of the oxo group, depends on its state of ionization. Hydrogen bonding to the sulfur by the solvent or the reagent will tend to increase the reactivity, as will protonation of the partly anionic thioxo sulfur atom. The very facile disubstitution^{448,449} of 2,4-dichloropyrimidine with aqueous or alcoholic sodium hydrosulfide involves less the reactivity of the intermediate 2-chloropyrimidine-4-thione or its anion than it does the high nucleophilicity of the hydrosulfide ion. An indication of this nucleophilicity is the reactivity²³² of the chloropyrimidinones toward hydrosulfide but not hydroxide ion. Due to deactivating anionization, 4,6-dichloropyrimidines on boiling with excess alkali^{450,451} yield only 6-chloro-4-pyrimidinones. The reaction of 2,4- and 4, 6-dichloro-5-aminopyrimidines with hydrosulfide ion stops at mono substitution⁴⁵² due to the deactivated state of the (anionized?) substrates. However, substitution of 2,4,6-trichloropyrimidine with this reagent spontaneously goes to completion⁴⁵³ with heat evolution. The 4-thioxo

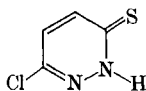
group in pyrimidine-2,4-dithione (**226**) and in 1-methyl-2-oxo-pyrimidine-4-thione (1-methyl-4-thiouracil) (**227**) is displaced by ammonia or amines,^{21p} again displaying the superior reactivity in (**226**) of *para*-activated leaving groups. The reactivity of halo-"mercapto"-pyridazines, such as **228**, has been investigated.⁴²⁵



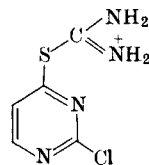
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[228]



[229]

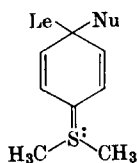
Disubstitution of 2,4-dichloropyrimidine with thiourea⁴⁵⁴ proceeds more readily than with hydrosulfide ion, principally because the former intermediate (**229**) contains the activating, cationic *acylated thio group* compared to the highly anionized mercapto group in the latter reaction.

A deactivating effect of the *thiocyanato* group is suggested by certain syntheses, but, under comparable circumstances, this group should be more activating than an alkylthio group. 2-Chloro-4-thiocyanatopyrimidine⁴⁰⁰ is formed from the dichloro compound and thiocyanate ion in boiling ethanol; surprisingly, 4-substitution^{338, 455} is favored even in 2,4-dichloro-5-nitropyrimidine, under milder conditions, of course. Relatively poor reactivity of the thiocyanato group in 2-chloro-4-thiocyanatopyrimidine is suggested by its stability (to attack by sulfur in the —N=C=S group of the product) during rearrangement to the isothiocyanate in boiling toluene.⁴⁰⁰

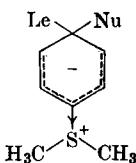
Sulfonio groups are very powerful activating substituents³¹⁵ which stabilize a negative charge by resonance through expansion⁴⁵⁷ of the sulfur valency shell (intermediate complex **230**) rather than by induction (**231**) as in trimethylammonio compounds. Miller and co-workers³¹⁵ observed a 10–50-fold increase in the rate of methoxydehalogenation of 4-substituted 2-nitrohalobenzenes for a dimethylsulfonio as compared with a trimethylammonio substituent. Significantly for this explanation of its effect, the faster rate was entirely due to a substantially lower energy of activation for the sulfonio compound. The lowering of the activation energy was almost as great as that produced by a 4-nitro group and definitely greater than that observed for a 4-acetyl group. The superiority of sulfonio over ammonio

activation is seen in the facile addition of nucleophiles to diethylsulfonioethylene while the triethylammonio analog is unreactive.⁴⁵⁶

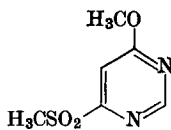
The activating effect of *methylsulfonyl groups* is clearly evident in 3-chloro-6-methylsulfonylpyridazine whose chlorine is displaced by sulfanilamide anion much more readily than that in the 6-methyl or 6-chloro analogs.²⁵⁴ Resonance electron donation by the chlorine to the methylsulfonyl group, cf. **103** and **104**, serves to activate the former and to deactivate the usually more reactive methylsulfonyl group.^{263a, 264} The effect of conjugation of *para* substituents is more clearly indicated in 3-methoxy-6-methylsulfonylpyridazine; the



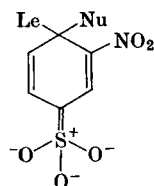
[230]



[231]



[232]



[233]

usually unreactive²⁵⁴ 3-methoxy group in 6-chloro-, 6-methyl-, or 6-methoxy-pyridazines is activated and displaced while the usually reactive methylsulfonyl group reacts to only a small extent (about 5%). Where conjugation between the two groups cannot occur, as in 4-methoxy-6-methylsulfonylpyrimidine (**232**), the methoxy group remains relatively unreactive to sulfanilamide anion in spite of the inductive effect of the methylsulfonyl group.²⁶³ The reactivity of the latter in **232** is still high in spite of indirect deactivation by a methoxy group^{263a} or even by two methoxy groups as in 2,4-dimethoxy-6-alkylsulfonylpyrimidines.^{264, 322, 323} An *ortho* or *para* sulfonyl group can stabilize the negative charge resulting from nucleophilic substitution in two ways: inductive stabilization of charge on a ring-carbon (**103**) and resonance-stabilization (**104**). The nitro group acts in two ways also, but resonance stabilization is the more effective. The sulfones utilize *d*-orbitals or hybrid *pd*-orbitals by expanding the valence shell of sulfur.^{444c, 445a} The activating effect of nitro groups is considerably greater (10–20 times as much increase in the rate) than that of methylsulfonyl groups in kinetic studies in chlorobenzenes or 2-nitrochlorobenzenes (alcoholic ethoxide or methoxide).^{54g, 458} The activating effect of a methylsulfonyl group in the reaction of 4-substituted 2-nitrochlorobenzenes with methanolic methoxide³¹⁴ is in

the following relation: $\text{N}_2^+ > \text{NO}_2 > \text{SO}_2\text{Me} > ^+\text{NMe}_3 > \text{COMe} > \text{H}$. Either a nitro or methylsulfonyl group in the *meta*-position produces a large activating inductive effect, as in **142**, and, when located at the *ortho*- or *para*-position the rate increase is one or two orders of magnitude greater. The difference in reactivity between *ortho* and *para* methylsulfonyl groups was not great in this work; in similar studies using methoxide or piperidine as reagents, Ogata and Tsuchida⁴⁵⁹ found the *ortho* substituted compound somewhat more reactive.

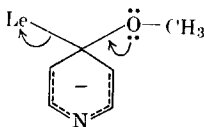
The activating effect of *sulfonate and sulfamoyl groups* is primarily the result of resonance stabilization of charge (intermediate complex **233**), even when the substituent is anionic (e.g., SO_3^- , SO_2NH^-). For methoxy-dechlorination of 4-substituted 2-nitrochlorobenzenes, the rates^{165, 460} relative to hydrogen are: $-\text{SO}_3^-$ 32; $-\text{SO}_2\text{NH}^-$ 50; $-\text{SO}_2\text{NMe}_2$ 26,000; $-\text{SO}_2\text{Me}$ 53,000; $-\text{SO}_2\text{C}_6\text{H}_5$ 76,000. In this $-\text{SO}_2\text{X}$ series, the activating effect decreases with increasing electron donation of X, as in the $-\text{COX}$ substituents, which are less activating. Anionic sulfonate ($-\text{SO}_3^-$) is more activating than the carboxylate anion.¹⁶⁵ Heppollette and Miller³¹⁴ have also compared the effect of different sulfamoyl groups. The activating effect of an alkylsulfonyl group is substantially increased by perfluorination to $-\text{SO}_2\text{CF}_3$ as noted above.^{421a, 421c, 421d}

F. DIRECTIVE EFFECT OF THE NUCLEOPHILE

The effects of the nucleophile on aromatic substitution which are pertinent to our main theme of relative reactivity of azine rings and of ring-positions are brought together here. The influence of a nucleophile on relative positional reactivity can arise from its characteristics alone or from its interaction with the ring or with ring-substituents. The effect of different nucleophiles on the rates of reaction of a single substrate has been discussed in terms of polarizability, basicity, "alpha effect" (lone-pair on the atom adjacent to the nucleophilic atom), and solvation in several reviews^{54c, g, 77d, e} and papers.^{124, 125a, 461} Parker⁴⁶² has suggested that the presence of a lone-pair on the entering group in the intermediate complex (**234**) increases the rate by assisting in breaking the bond to the leaving group (Le) as indicated.

In many cases, the effects of the nucleophile observed with carbocyclic aromatics can be expected to carry over to heteroaromatics, e.g., changing the relative reactivity of leaving groups (Section II, D, 2, b); deceleration by charge-transfer complexing with the substrate

(Section I, D, 1); acceleration by hydrogen bonding to the leaving group (Section I, D, 2, d); deceleration by reversible or irreversible modification of a substituent (Section II, D, 1); (aliphatic S_N2) demethylation of methoxy (Section II, D, 2, e), trimethylammonio (Section II, D, 2, c), or dimethylsulfonio groups.⁴⁶³



[234]

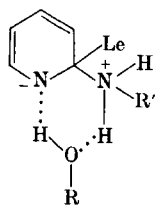
Substitution at the most electron-deficient *ortho*-position of azines by alkali amides or organometallics has been attributed^{156, 187a} to a combination of a highly reactive nucleophile and substrate while others have predicted and observed loss of selectivity^{135, 157, 158} from such combinations. An alternative explanation (Section II, B, 5) based on a cyclic transition state (cf. **75**) formed from the substrate and the ion-paired reagent seems reasonable. When not ion-paired, as in **75**, carbanions and amide ions should react fastest at the positions where other anions do. Their rate of *ortho* substitution, relative to the methoxide ion, might be greater due to the lack of lone-pair repulsions (cf. Section II, B, 2, a) or to electrostatic attraction (cf. this effect in Table II, p. 270) if concurrently there is appreciable electrophilic attack at the azine-nitrogen by the metal cation. Where substitution of hydrogen is involved, the relative rates at different positions can be affected by the relative equilibrium concentrations of the intermediate complexes and their relative rates of loss of hydride ion due to electrophilic attack by the metal cation or by an oxidizing agent at the hydrogen atom. However, the elimination of hydride ion was not important in orienting substitution of pyridines with phenyllithium.^{187c} Amination at a *peri*-position in azanaphthalenes by NH_2^- is possible through a cyclic transition state, but the activation produced by the partial cationization (electrophilic attack of the metal cation at the azine-nitrogen) is considerably diminished in transmission to the adjacent ring (Section IV).

In addition to the effects of a cyclic transition state, of lone-pair repulsions, and of rate of removal of hydride ion mentioned above, the position of nucleophilic substitution can be altered by (a) hydrogen

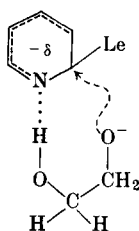
bonding of the nucleophile with an azine-nitrogen, with the leaving group, or with a substituent, (b) the nature of the nucleophile in relation to protonation or cationization of an azine-nitrogen, (c) variation of electrostatic effects dependent on the nucleophile, (d) London forces interaction of the nucleophile with the leaving group or a nearby substituent, (e) steric effects, and (f) intramolecular substitution when the nucleophilic atom is part of a substituent. These factors are discussed in sequence below.

Hydrogen bonding (cf. **213** and **214**) of nucleophiles to the oxo substituent in azinones is postulated in Section II, E, 2, e to explain the substantial reactivity of their derivatives. In aminations of azines, reactivity at an adjacent carbon can be accelerated by proton transfer in the intermediate complex proceeding through direct hydrogen bonding between the two nitrogen atoms or through mediation by solvent (**235**) (cf. **46**, **47**, and **59**). Hydrogen bonding of the nucleophile or its conjugate acid to an azine-nitrogen (cf. **62** and **236**) can favor reaction at an adjacent or a *peri*-position by an increase in the entropy of activation for this position. These two effects of hydrogen bonding can occur also in azine *N*-oxides.

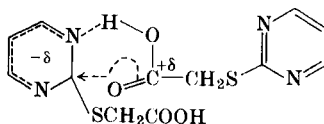
Factor *b* above is discussed in Sections II, B, 1; II, B, 4; and II, C. A hydrogen-bonded structure such as **221** can account for the facile reaction of 5-bromouracil or for the unique, so-called hydrolyzability of carboxymethylthio-azines (**237**). The latter may also react via the intramolecular mechanism indicated in **136**. The hydrogen-bonded transition state **238** seems a reasonable explanation of the fact that 3,4,6- and 3,4,5-trichloropyridazines react with glacial acetic acid selectively to give 3-pyridazinones⁴⁶⁴ while other nucleophiles (alkoxides, hydrazine, ammonia, or sulfanilamide anion) react at the 4- and 5-positions.^{434b} In this connection, 4-amino-3,5-dichloropyridazine in liquid hydrazine gives (95°, 3 hr, 60% yield) the "isomer-



[235]

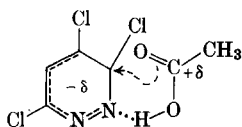


[236]

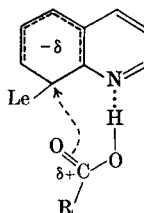


[237]

free" 3-hydrazino analog.^{434c} Predominant hydrogen bonding to the more basic ring-nitrogen in **238** leads to the 3-pyridazinone (yield only 35%); the minor isomeric hydrogen-bonded transition state may have led to some unisolated 6-pyridazinone. Hydrogen bonding of the protonated substrate to acetate ion or acetic acid is equivalent to **238**, but the more basic products would predominantly bind the liberated HCl. Of the isomeric hydrogen-bonded transition states of 3,4,5-trichloropyridazine, only the one involving the less basic 2-nitrogen atom is adjacent to a suitable leaving group. Reactions at a *peri*-position in azanaphthalenes might be facilitated by the analogous structure **239**.



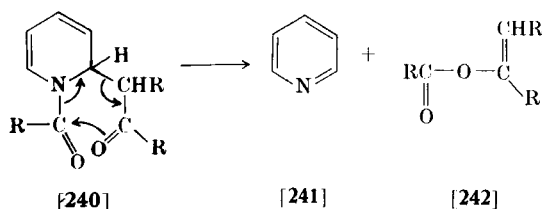
[238]



[239]

The variation of position of substitution caused by electrostatic effects involving the nucleophile is included in Sections I, D, 2, II, B, 1, and II, B, 4. An anionic nucleophile will tend to react more readily adjacent to a cationic azinium-nitrogen than to an azine-nitrogen while an uncharged nucleophile (becoming positive in the transition state) will do so less readily. An entropy of activation effect or "built-in" solvation (Section I, D, 2, b) is involved in reaction of 2-nitrochlorobenzenes with amines.^{77b, 97c, 97d} This effect has been noted in nitro-pyrimidines and -pyridines in which amination displaces substituents adjacent to the nitro group in preference to those in other activated positions (see Section II, E, 2, c). Reissert compounds¹⁴⁹ form at the 2-position apparently because of a combined effect of electrostatic attraction between the intermediate cationic *N*-acyl azinium substrate and cyanide anion plus interaction of the partly anionic acyl oxygen with the partly cationic carbon of the cyano group in the transition state. When an *N*-acylpyridinium compound reacts with an enolate anion, the intermediate complex is sterically suited (cf. **240**) for *O*-acylation¹⁴⁹ which reverses the nucleophilic addition

step forming **241** and **242**. The 4-adduct is not susceptible to this sterically-controlled acylation, and 4-substitution occurs if the oxidizability (loss of hydride ion) is sufficient.

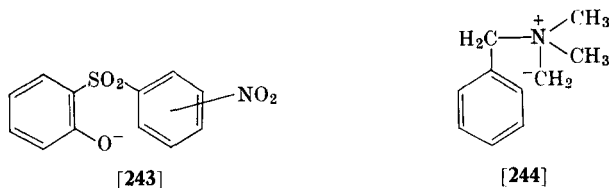


The accelerative effect of London forces of attraction^{2b} between a nucleophile and nearby substituents has been investigated in quinoline and benzene derivatives by Bunnett and co-workers.^{51, 52, 117b, 307} In 2-, 4-, and 6-arylsulfonyl-3-nitrochlorobenzene, Loudon and Shulman⁴⁶⁵ found that arylmercaptide ion, presumably through this effect, displaced the arylsulfonyl group while methoxide or ammonia displaced the nitro or chloro group.

As the size of the nucleophile increases, reaction adjacent to a solvated azine-nitrogen or to a quaternized ring-nitrogen will be sterically hindered. The very large decelerative effect^{80a, 110} of solvation of the nucleophile in aromatic substitution is mentioned in Section I, D, 2, d.

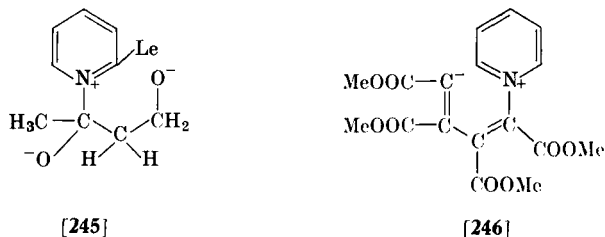
When the nucleophilic atom is part of a substituent attached to the ring, the position of intramolecular attack will be determined by the ring sizes of the possible transition states as well as by the more general pattern of positional reactivity and the effect of the leaving group. Ring closure by nucleophilic attack at a *peri*-position can also be favored by such substituents. Nucleophilic displacements or ring closures via nucleophilic attack can also occur intramolecularly with substituents on azine-nitrogen. In such instances, the azine-rings are activated in all positions, but especially *ortho* and *para* to the azinium-nitrogen. Generally, only reaction *ortho* or *peri* to the substituent nucleophile will be appreciably accelerated. Similar sterically-controlled intramolecular nucleophilic aromatic substitutions have been observed in carboaromatics: the Smiles rearrangement^{77a} of compounds such as those bearing a 2-hydroxybenzenesulfonyl group attached to an activated position of another benzene ring (**243**) to the corresponding 2-(nitrophenyloxy)benzenesulfinate ion and the Hauser rearrangement^{466, 467a} of arylmethylammonium ylides such as **244**

to the corresponding 2-(dimethylaminomethyl)toluene. An example of an almost unactivated aromatic position (bearing a nitro group, an excellent leaving group) being substituted intramolecularly by a relatively weak nucleophile has been reported recently^{353b}: 2'-nitro-biphenyl-2-carboxylate cyclizes to 3,4-benzocoumarin; cf. ring closure



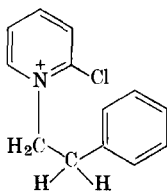
of a 2-nitro-2'-hydroxystilbene.^{467b} A Smiles rearrangement of 4-(*o*-aminophenylthio)pyrimidines to 4-(*o*-mercaptophenylamino)-pyrimidines in acid was suggested^{442c} to explain their forming identical pyrimidobenzothiazines.

Reversible interaction of the carbonyl group with an azine lone-pair (cf. **245**) should facilitate substitution adjacent to the heteroatom by the anion of a β -hydroxyethyl ketone. A similar cyclic intermediate (**246**) is presumably responsible for the cyclization of acetylene dicarboxylic esters with azines.⁴⁶⁸ Similar cyclic intermediates

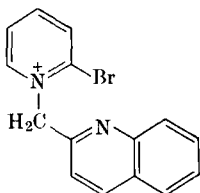


favoring 2-substitution can be formed from *N*-alkylation⁴⁶⁹ of pyridine with ethylene oxide, β -propiolactone, or 2-hydroxyethanesulfonic acid sultone.

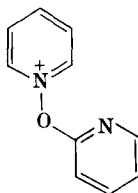
Ring closure of 2-chloro-1-phenethylpyridinium ion (**247**) (prepared *in situ*) to 1,2-dihydro-3,4-benzoquinolizium²³⁷ ion involves intramolecular nucleophilic displacement of the chloro group by the phenyl π -electrons. A related *intermolecular* reaction involving a more activated pyridine ring and more nucleophilic π -electrons is the formation of 4-(*p*-dimethylaminophenyl)pyridine (and benzaldehyde) from dimethylaniline and 1-benzoylpyridinium chloride⁴⁷⁰ (cf. Section III, B, 4, c).



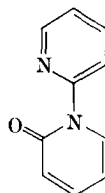
[247]



[248]



[249]



[250]

Intramolecular nucleophilic displacement of the bromo group by an azine-nitrogen occurs in the cyclization⁴⁷¹ of *N*-2-quinaldyl-2-bromopyridinium bromide (**248**) to give the naphthoimidazopyridinium ring system. The reaction of 2-bromopyridine and pyridine 1-oxide yields 1-(2-pyridoxy)pyridinium bromide^{472, 473} (**249**) which readily undergoes an intramolecular nucleophilic substitution in which departure of hydrogen as a proton presumably facilitates the formation of **250** by loss of the *N*-oxypyridyl moiety.

III. Monocyclic Azines. Relative Reactivity of Rings and Ring-Positions

A. GENERAL INTERRELATION AND KINETIC DATA

1. Interrelation of Reactivity of Rings and Ring-Positions. Reactivity Rules

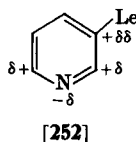
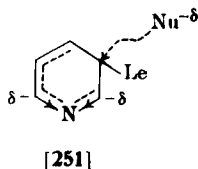
The effect of an azine-nitrogen on the reactivity of a substance toward nucleophiles is a combination of lowering the energy of repulsion on the nucleophile by the π -electrons and of stabilizing the negative charge donated to the azine system by the nucleophile. A decrease in the energy of activation of the nucleophilic substitution results. In a series of reactions, the relative reactivity derived from the activation energy (E_A) and from reaction rates will not always be the same. The change in entropy of activation may oppose (Compensation Law^{152a-152c}) the effect of E_A on the rate, reinforce its effect, or by itself control the rate change. Therefore, relative degrees of *activation* by an azine-nitrogen are probably best evaluated by means of the activation energy. In the cases where changes in the entropy of activation control the relative reaction rates, it seems pertinent to consider that *activation in the same sense* is still reflected in the energy of activation. This approach for azines yields a reasonably consistent

scheme of relative reactivity upon which one can superimpose a scheme of specific alterations arising from entropy of activation or intramolecular effects. Nonetheless, the rates have considerable theoretical and practical interest of their own and, in some cases, are the only parameters whose variation is greater than experimental error.

Conclusions and predictions concerning the reactivity of monocyclic azines are derived from three sources: (a) the kinetic data of Section III, A, 2, (b) qualitative or semi-quantitative comparisons in preparative organic chemistry (Section III, B), and (c) theoretical considerations presented in Section II, B. Reactivity can be described by four generalizations:

- (1) activation by an *ortho* or *para* (to the leaving group) azine-nitrogen via resonance stabilization of charge is much greater than by a *meta* azine-nitrogen acting by inductive stabilization;
- (2) activation by a *para* azine-nitrogen is greater than that by an *ortho* azine-nitrogen; however, the relative *rate* of reaction at an *ortho*-position can be appreciably accelerated by intervention of electrostatic interactions, hydrogen bonding to an azine-nitrogen, or cyclic transition states;
- (3) combined activation by a *para* plus an *ortho* azine-nitrogen is greater than that by two *ortho* azine-nitrogens; and
- (4) activation by a *meta* azine-nitrogen is substantial.

The first generalization is illustrated by the behavior of the 2- and 4- vs. the 3-derivatives of pyridine, the second by the reactivity of 4- vs. 2-substituted pyridines, the third by the relation of 4- vs. 2-derivatives of pyrimidine, and the fourth by the appreciable reactivity of 3-substituted pyridines or 5-substituted pyrimidines compared to that of their benzene analogs. Various combinations of azine-nitrogens in other poly-azines supply further examples. Theoretical aspects of (1), (2) and (3) are discussed in Section II, B, 2. The effect involved in (4) is believed to be more the result of the inductive stabilization of an adjacent negative charge in the transition state (cf. 251) than of the electron deficiency created in the ground state (cf. 252). The quantitative relation between inductive stabilization and resonance stabilization is not precisely defined by available data. However, a



rough estimate can be made by comparison of the ratios of the rates of piperidino-dechlorination (Tables II, III, and IV, cf. pp. 270, 272, and 273, respectively) of 2-chloropyrazine:2-chloropyridine (ca. $10^3:1$) and of 2-chloropyrimidine:2-chloropyridine (ca. $10^6:1$). This comparison suggests that two *meta* azine-nitrogens will have an effect about equivalent to one *ortho* azine-nitrogen. The recent synthesis of 5-bromopyrimidine⁴⁷⁴ and its substantial reactivity toward methoxide and ethylmercaptide ions suggest that its activation can be compared with that of the bromopyridines. In nitrohalobenzenes,⁷⁴ two *meta* nitro groups were found to have an accelerative effect on halogen displacement equal to that of one *ortho* or *para* nitro group.

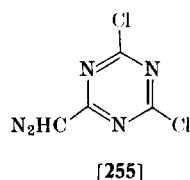
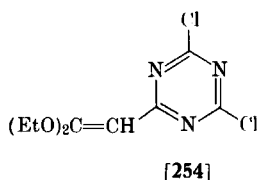
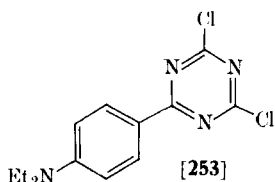
From kinetic data and preparative organic chemistry, the following relations between the reactivity of azine positions can be deduced:

ortho to azine-N: 2-*s*-triazinyl > 2-pyrimidinyl > 3-pyridazinyl \cong pyrazinyl > 2-pyridyl;

para to azine-N: 4-pyrimidinyl > 4-pyridazinyl > 4-pyridyl;

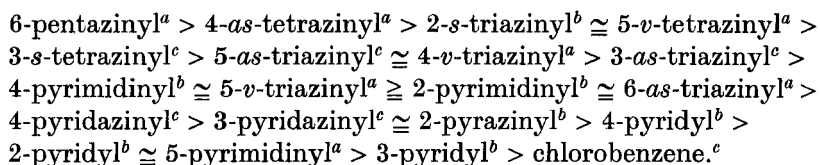
para vs. *ortho* to azine-N: 4-pyridazinyl > 3-pyridazinyl.

By analogy with 4- and 2-chloropyrimidines, it is reasonable to predict the relation: 5-*as*-triazinyl > 3-*as*-triazinyl. The substantial activation by additional ring-nitrogens, especially in the optimal 1,3,5 arrangement, is evident in the fact that chloro-*s*-triazines, even when *deactivated* by one or two substituents, are equally or more reactive than many chloro-azines or chloro-diazines. For example, 2,4,6-trichloro-*s*-triazine reacts with various nucleophiles⁴⁷⁵ to give monosubstituted derivatives at 0–10°, disubstituted at 20–30°, and trisubstituted at 50–70°. The reactivity of the *s*-triazine system is so great that the trichloro derivative undergoes nucleophilic substitution by the phenyl π -electrons of diethylaniline⁴⁷⁶ (forming **253**), by the ethylenic



double bond of ketene diethylacetal^{477a} (forming **254**), and by diazomethane³⁶⁸ (forming **255**). The more activated polyazines are expected to undergo these interesting reactions also.

The following sequence of reactivity of monocyclic azines toward nucleophiles includes a number of postulated relations based on analogy and on theoretical considerations:

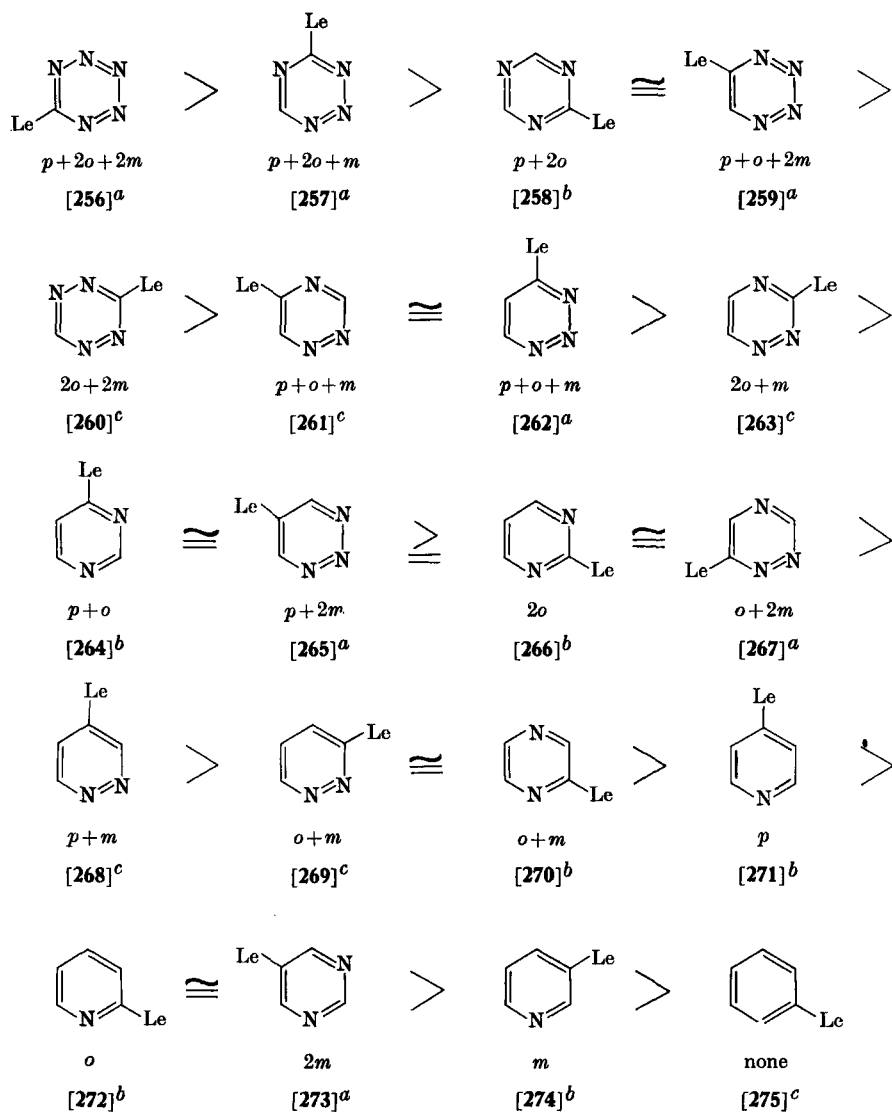


This sequence is presented by structural formulas in Scheme I, where the designations " $p + 2o + m$," etc., refer to the number and position (*para*, *ortho*, *meta*) of the activating ring-nitrogens relative to the leaving group (Le). The azinyls marked with a superscript " a " are in predicted locations. There is kinetic data available on those marked with a superscript " b " and synthetic organic comparisons on those marked with superscript " c ."

It should be noted that positional selectivity is never complete even when a "clean" reaction gives only one isolated product.^{477b} Reaction occurs at all positions in proportion to the ratio of the rate constants. The difference between a "clean" reaction (e.g., rate 9 times that of a competing reaction) and one giving a troublesome mixture can be merely a moderate quantitative increase in one rate (e.g., to a 9:7 rate ratio) or a change in both rates (e.g., to a 3:4 ratio). Work such as that of Kauffmann and Boettcher³⁵ on heteroarynes illustrates the potential of modern forms of chromatography for determining the true proportion of even very minor products.

Relative reactivity will vary with the temperature chosen for comparison unless the "temperature coefficients" are identical. For example, the rate ratio of ethoxy-dechlorination of 4-chloro- vs. 2-chloro-pyridine is 2.9 at the experimental temperature (120°) but is 40 at the reference temperature (20°) used for comparing the calculated values.^{55, 478} The ratio of the rate of reaction of 2-chloro-pyridine with ethoxide ion to that of its reaction with 2-chloronitrobenzene is 35 at 90° and 90 at 20°. The activation energy determines the "temperature coefficient" which is the slope⁴⁷⁹ of the line relating the reaction rate and temperature. Comparisons of reactivity will of course vary with temperature if the activation energies are different and the lines are not parallel. The increase in the reaction rate with temperature will be greater the higher the activation energy.

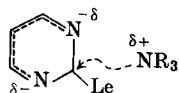
SCHEME I



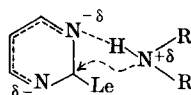
Comparisons of reactivity at different temperatures may be misleading if the Compensation Law or isokinetic relationship applies.^{152a-152c} In a series of reactions for which an *accelerative* decrease in the activation energy is accompanied by a *decelerative* decrease in the entropy of activation⁴⁸² (Compensation Law^{152a}), or the two increase together, there will be an isokinetic temperature^{152b} (between 0–200°C for three-fourths of the 79 reactions tabulated by Leffler^{152b}). The rate vs. temperature curves for all the reactions in the series pass through this single point. Comparisons are affected since the isokinetic temperature is a point of *inversion of relative reactivity* in the series.^{152c} It is also a point of change in control of the reaction rate by the energy of activation below it to control by the entropy of activation above it. The effect of changes in structure, solvent, etc., will depend on the relation of the experimental temperature to the isokinetic temperature. A practical consequence of knowing the isokinetic temperature is the possibility of “cleaning up” a reaction by adjusting the experimental temperature. Reactions are cleaner at lower temperatures (as often observed) if the decrease in the experimental temperature makes it farther from the isokinetic temperature. The isokinetic relationship or Compensation Law does not seem to apply widely to the data herein, and, in any case, comparisons are realistic if made far enough from the isokinetic temperature.

The order of reactivity in Scheme I holds for anionic nucleophiles in general. Very little comparative information and no kinetic data are available for nucleophiles in which the nucleophilic atom carries a partial positive charge (e.g., the sulfur atom of sulfinic, sulfite, and sulfoxide groups). A shift in the relative reactivity of 4- vs. 2-substituted azines is expected when certain effects can intervene and increase the rate of reaction at the 2-position. One such effect is the electrostatic attraction between an anionic nucleophile and a cationic substrate which leads to a large accelerative change in the entropy of activation, with the greatest effect being at the position *ortho* to the cationic center. The rates of reaction of 2- and 4-chloro-1-methylpyridinium salts (Table II, p. 270) with a phenoxide anion¹⁸¹ are controlled by this effect (cf. 281) in spite of an activation energy more favorable to the 4-isomer. Relative to the chloropyridines, both isomers are enormously more reactive. Note that the cationization in the chloropyridine *N*-oxides produces a large acceleration of the reaction of all of three isomers, relative to the chloropyridines, with methoxide and with piperidine (cf. Table II). The mechanistic aspects of reversible

and irreversible cationization are discussed in Section II, B, 4 and general aspects in Section II, C. A related effect is electrostatic attraction between unlike charges in the zwitterionic transition states (276) arising from uncharged nucleophiles such as tertiary nitrogen bases (e.g., pyridine and trimethylamine). In other aminations, this attraction can be accompanied by stabilization due to hydrogen bonding (277) of the amine to an azine-nitrogen which can facilitate



[276]



[277]

reaction also through completing the proton transfer in 277 or in a solvent-mediated fashion (235). The significance of this "N—H factor" will be decreased or removed when a strong base is present. There is a need for kinetic comparison of amination vs. alkoxylation and of secondary amination vs. tertiary amination using 2- and 4-substituted pyridines, pyrimidines, and other nitrogen-containing heterocycles in order to explore both facets of this effect (in aminations of nitrohalobenzenes,^{97f} the hydrogen bonding is the more significant, see Section I, D, 2, b).

From the work of Chapman *et al.*⁴⁰³ on 2-chloro-5-nitropyridine (Table VII, p. 276) and 2,4-dinitrochlorobenzene (Table VIII, p. 277), a small electrostatic effect (same ratio of *ortho* azine-N:*ortho* NO₂ effects for reactions with pyridine and with piperidine) and an appreciable hydrogen-bonding effect (anilines react much faster than pyridine bases) are indicated. Stronger hydrogen bonding to an *ortho*-nitro group was considered⁴⁰³ to be responsible for the greater rate and lower activation energy of reaction of 2,4-dinitrochlorobenzene with primary or secondary amines compared to tertiary bases. Regardless of the substrate, the hydrogen-bonding effect has to overcome the 3–6 kcal resonance energy lost when the anilines react.⁴⁰⁴ A change from a conjugated partly *sp*²-hybridized nitrogen in the nucleophile to a *sp*³-hybridized nitrogen in the transition state is required in the reaction of anilines but not of pyridine bases. Consistent with Chapman's hydrogen-bonding interpretation^{403,404} is the fact that the magnitude of the energy difference is comparable to that of hydrogen bonding (Section II, C) and the lack of such a large difference between aniline and pyridine in their reactivity toward phenacyl chlorides.⁴⁸⁰

The effect of hydrogen bonding to nuclear substituents in transition states is reviewed in Sections I, D, 2, b, and II, E. Relative reactivity at different ring-positions is postulated to be alterable by hydrogen bonding of an azine-nitrogen to the solvent or to the reagent (Section II, B, 3 and III, B). However, there appears to be no kinetic data relevant to this postulate.

Another such effect is the intervention of cyclic transition states in reactions of organometallic compounds (Section II, B, 5) with azines or in intramolecular nucleophilic substitutions (Section II, F).

Relative reactivity of ring-positions based on "positional selectivity" of polychloro-azines must be regarded with caution because of the unequal activating effects of the chlorine substituents on each other. Also, it should be emphasized that one cannot use the positional selectivity in di- and tri-substitutions to assess relative reactivity of different positions. In such substitutions, the reactivity is determined by a complex combination of activating and deactivating effects which are unequal at the ring-positions (cf. Sections II, E, 1, II, E, 2, c, and II, E, 2, e).

2. Kinetic Data on Nucleophilic Substitution of Monocyclic Azines

In spite of the extensive kinetic work of Chapman and co-workers, much remains to be done on the reactivity of azines with nucleophiles. The data available on substitution by alkoxide ions are especially meager. The missing information on alkoxide reactions should give a better picture of the activation of different ring-positions than is possible with the data on aminations. The latter include the effects shown in 235, 276, and 277 in addition to activation by the azine-nitrogens.

The available data are arranged by ring and ring-position in Tables II-VIII. The rate coefficients have been recalculated to the same units, where necessary; the fact that different temperatures of reference were used in the publications should be noted. The temperatures used experimentally for a given substrate were chosen for a rate of reaction which was convenient to measure, and then for comparison, rate constants were calculated at a common temperature by means of the standard equations^{479, 481, 482} (cf. discussions by Ingold⁴⁸³ and by Gould⁴⁸⁴). Consistent bimolecular rate constants at various concentrations and times were found except in cases of autocatalysis. For the rate equations used and details on the limits of error,⁴⁸⁵ the reader is referred to the original publications.^{55, 73, 167, 403, 404, 475, 486a, 486b, 486c}

TABLE II
PYRIDINES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTION

Line No.	Pyridine substituents	Nucleophile (solvent)	Rate constant ^a (temp. °C) 10 ⁶ <i>k</i> liter mole ⁻¹ sec ⁻¹	Activation energy ^b kcal mole ⁻¹	Entropy of activation ^c cal mole ⁻¹ deg ⁻¹	Frequency factor ^d log ₁₀ A	Ref.
1	2-Cl	EtO ⁻ (EtOH) ^e	(20°) 2.2 × 10 ⁻³	26.8 ^f	-9.2	11.4	55, 639
2	2-Cl	piperidine (EtOH)	(20°) 4.8 × 10 ⁻⁴	19.9 ^f	-35.8	5.6	55
	2-Cl	piperidine (MeOH)	(80°) 0.15	23.0	—	7.4	486d
3	2-Cl	piperidine (solvent) ^g	—	17.1	-42.2	—	487
4	4-Cl	EtO ⁻ (EtOH)	(20°) 8.7 × 10 ⁻²	20.9 ^f	-22.3	9.3	55, 139
	4-Cl	piperidine (MeOH)	(80°) 1.64	17.0	—	4.8	486d
5	2-Cl-1-Me	4-NO ₂ C ₆ H ₄ O ⁻ (MeOH)	(50°) 1.39 × 10 ⁷	18.6	+4.7	14.3	131
6	2-Cl-1-Me	MeO ⁻ (MeOH)	(-15°) very fast ^h	—	—	—	131
7	3-Cl-1-Me	4-NO ₂ C ₆ H ₄ O ⁻ (MeOH)	(50°) 0.28	30.2	+2.8	13.9	131
8	3-Cl-1-Me	MeO ⁻ (MeOH)	(50°) ca. 100	—	—	—	131

9	4-Cl-1-Me	4-NO ₂ C ₆ H ₄ O ⁻ (MeOH)	(50°) 4.6×10^5	17.6	-7.8	11.6	131
10	4-Cl-1-Me	MeO ⁻ (MeOH)	(-15°) very fast ^a	—	—	—	131
11	2-Cl	MeO ⁻ (MeOH)	(50°) 3.31×10^{-2}	28.9	-5.3	12.1	486b
12	3-Cl	MeO ⁻ (MeOH)	(50°) 1.09×10^{-5}	32.9	-9.2	11.3	486b
13	4-Cl	MeO ⁻ (MeOH)	(50°) 0.89	25.2	-10.4	11.0	486b
14	2-Cl-1-oxide	MeO ⁻ (MeOH)	(50°) 6.4×10^2	20.3	-12.4	10.6	486b
15	2-Cl-1-oxide	piperidine (MeOH)	(80°) 4.05×10^2	15.0	—	5.9	486c, d
16	3-Cl-1-oxide	MeO ⁻ (MeOH)	(50°) 1.16	24.6	-11.7	10.7	486b
17	3-Cl-1-oxide	piperidine (MeOH)	(80°) 0.104	—	—	—	486c
18	4-Cl-1-oxide	MeO ⁻ (MeOH)	(50°) 1.00×10^3	19.0	-15.6	9.9	486b
19	4-Cl-1-oxide	piperidine (MeOH)	(80°) 1.11×10^2	13.6	—	4.5	486c, d

^a Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperature given in parentheses.

^b The Arrhenius activation energy,⁴⁷⁹ E_A .

^c Entropy of activation,⁴⁸² ΔS^\ddagger .

^d The Arrhenius frequency factor,⁴⁷⁹ A , is in units of liter mole⁻¹ sec⁻¹.

^e Water was added to absolute ethanol to make 99.8% ethanol.

^f Values of ΔH^\ddagger were also given.

^g Carried out in this substance as solvent.

^h Quantitative formation of chloride ion occurred within 2 min.

TABLE III
PYRIMIDINES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTION

Line No.	Pyrimidine substituents	Nucleophile in 99.8% EtOH ^a	Rate constant ^b (temp. °C) 10 ⁶ <i>k</i> liter mole ⁻¹ sec ⁻¹	Activation energy ^c kcal mole ⁻¹	Entropy of activation ^d cal mole ⁻¹ deg ⁻¹	Frequency factor ^e log ₁₀ A	Ref.
1	2-Cl	EtO ⁻	(20°) 1.63 × 10 ³	16.9 ^f	-15.7	—	55
2	2-Cl	piperidine	(20°) 3.34 × 10 ² (30°) 6.70 × 10 ²	12.4 ^f —	-34.3 —	5.7 —	55, 167 55, 167
3	2-Cl	piperidine	(50°) 2.43 × 10 ³	10.6	-37.2	—	487
4	2-Cl	piperidine ^g	(50°) 3.61 × 10 ²	11.5	-44.4	—	487
5	2-Cl	morpholine	(30°) 1.52 × 10 ²	12.3	—	5.0	167
6	2-Cl-4-Me	piperidine	(30°) 2.80 × 10 ²	12.5	—	5.4	167
7	2-Cl-4-Me	morpholine	(30°) 69	13.0	—	5.2	167
8	2-Cl-4,6-Me ₂	piperidine	(30°) 1.13 × 10 ²	12.1	—	4.8	167
9	2-Cl-4,6-Me ₂	morpholine	(30°) 28	12.6	—	4.5	167
10	4-Cl ^h	piperidine	(20°) 1.4 × 10 ³	ca. 10.5 ^f	ca. -35.7	ca. 5.0	167
11	4-Cl-2-Me	piperidine	(30°) 3.0 × 10 ³	10.6	—	5.1	167
12	4-Cl-2-Me	morpholine	(30°) 7.7 × 10 ²	10.7	—	4.6	167
13	4-Cl-6-Me	piperidine	(30°) 2.14 × 10 ³	11.0	—	5.2	167
14	4-Cl-6-Me	morpholine	(30°) 5.55 × 10 ²	11.1	—	4.7	167
15	4-Cl-6- <i>t</i> -Bu	piperidine	(30°) 8.33 × 10 ²	11.0	—	4.9	488

^a Water was added to absolute ethanol to make 99.8% ethanol.

^b Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperature given in parentheses.

^c The Arrhenius activation energy,⁴⁷⁹ E_A .

^d Entropy of activation,⁴⁸² ΔS^\ddagger .

^e The Arrhenius frequency factor,⁴⁷⁹ A, is in units of liter mole⁻¹ sec⁻¹.

^f Values of ΔH^\ddagger were also given.

^g Reaction carried out in petroleum ether rather than in 99.8% EtOH.

^h Side-reactions prevented measurements on this substance; the values are approximations derived from data on the methyl derivatives, lines 11 and 13.

TABLE IV
PYRAZINES. KINETIC DATA ON PIPERIDINO-DEHALOGENATION

Line No.	Substrate substituents	Nucleophile (solvent)	Rate constant ^a (temp. °C) 10 ⁶ <i>k</i> liter mole ⁻¹ sec ⁻¹	Energy of activation ^b kcal mole ⁻¹	Entropy of activation ^c cal mole ⁻¹ deg ⁻¹	Ref.
1	2-Cl	piperidine (toluene)	(75°) 10	13.2	-50.4	487

^a Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperature given in parentheses.

^b The Arrhenius activation energy,⁴⁷⁹ E_A .

^c Entropy of activation,⁴⁸² ΔS^\ddagger .

TABLE V
PYRIDAZINES AND PYRIMIDINES. KINETIC DATA ON ANILINO-DECHLORINATION

Line No.	Substrate	Nucleophile in benzene	Rate constant ^a (temp. °C) 10 ⁶ <i>k</i> liter mole ⁻¹ sec ⁻¹	Ref.
1	3,6-Cl ₂ -pyridazine	aniline	(21.7°) 0.10	218
2	3,6-Cl ₂ -pyridazine	aniline + AcOH (1 <i>N</i>)	(21.7°) 0.93	218
3	3,6-Cl ₂ -pyridazine	aniline + AcOH (3 <i>N</i>)	(21.7°) 2.33	218
4	2,4-Cl ₂ -pyrimidine	aniline	(25°) 0.067	218
5	2,4-Cl ₂ -pyrimidine	aniline + AcOH (0.1 <i>N</i>)	(35°) 2.83	218
6	2,4,6-Cl ₃ -pyrimidine	aniline	(25°) 1.13	218
7	2,4,6-Cl ₃ -pyrimidine	aniline + AcOH (0.1 <i>N</i>)	(25°) 33.3	218

^a Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperature given in parentheses.

TABLE VI

s-TRIAZINES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTION

Line No.	Triazine substituents	Nucleophile + catalyst	Solvent	Rate constant ^a (temp. °C) 10 ⁶ <i>k</i> liter mole ⁻¹ sec ⁻¹	Kinetic parameters ^{b,c}		Ref.
					<i>E</i> _A	Δ <i>S</i> [‡]	
1	2,4,6-Cl ₃	aniline	benzene	(25°) 2.33 × 10 ⁵	—	—	218
2	2,4,6-Cl ₃	aniline + AcOH (0.02 <i>N</i>)	benzene	(25°) 2.73 × 10 ⁶	—	—	218
3	2,4-Cl ₂ -6-anilino	aniline	benzene	(25°) 1.75 × 10 ³	—	—	218
4	2,4-Cl ₂ -6-anilino	aniline + AcOH (0.05 <i>N</i>)	benzene	(25°) 7.55 × 10 ³	—	—	218
5	2,4-Cl ₂ -6-anilino	arylamines	tetrahydrofuran	(40°) 1.5 × 10 ³ –2.4 × 10 ⁴	8.0	–43	382
6	2,4-Cl ₂ -6-anilino	benzylamine	tetrahydrofuran	(40°) 9.31 × 10 ⁵	7.9	–36	382
7	2,4-Cl ₂ -6-substituted anilino	arylamines	tetrahydrofuran	(40°) 4.5 × 10 ² –2.2 × 10 ⁴	8.0–9.2	–42	382
8	2,4-Cl ₂ -6-NH ₂	arylamines	tetrahydrofuran	(40°) 4.7 3 × 10 ² –2 × 10 ³	13.1	–31	382
9	2,4-Cl ₂ -6-alkylamino	arylamines	tetrahydrofuran	(40°) 2 × 10 ³	10.1	–41	382
10	2,4-Cl ₂ -6-dialkylamino	arylamines	tetrahydrofuran	(40°) 4.9 1.5 × 10 ³ –2 × 10 ⁴	10.0	–41	382
11	2-Cl-4-anilino-6-alkoxy	benzylamine	tetrahydrofuran	(40°) 6 × 10 ³	—	—	382
12	2-Cl-4-anilino-6-NH ₂	benzylamine	tetrahydrofuran	(40°) 65	14.0 ^f	–33	382
13	2-Cl-4-anilino-6-substituted amino	benzylamine	tetrahydrofuran	(40°) 50–320 ^g	14.0 ^f	–36 ^f	382
14	2,4,6-Cl ₃	aniline + autocatalysis ^h	benzene	(25°) 2.2 × 10 ⁵	—	—	475
15	2,4,6-Cl ₃	aniline + bifunctional catalysts	benzene	(25°) 6–25 × 10 ⁵	—	—	475
16	2,4,6-Cl ₃	aniline + base catalysts	benzene	(25°) 6–26 × 10 ⁵	—	—	475
17	2,4-Cl ₂ -6-anilino	aniline + autocatalysis ^h	benzene	(25°) 2.5 × 10 ⁴	—	—	475
18	2,4-Cl ₂ -6-(<i>N</i> -Me-anilino)	<i>N</i> -Me-aniline	benzene	(50°) 3.7 × 10 ²	—	—	475
	2,4-Cl ₂ -6-(<i>N</i> -Me-anilino)	<i>N</i> -Me-aniline	benzene	(25°) 62	—	—	475
19	2,4-Cl ₂ -6-(<i>N</i> -Me-anilino)	<i>N</i> -Me-aniline + catalysts	benzene	(25°) 7 × 10 ²	—	—	475

^a Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperature given in parentheses, except for some of the catalyzed reactions (lines 1–4 and 14–19) which are third-order.

^b The Arrhenius activation energy,⁴⁷⁹ *E*_A, in kcal mole⁻¹.

^c Entropy of activation,⁴⁸² Δ*S*[‡], in cal mole⁻¹ deg⁻¹.

^d Rates increase with the basicity of the anilines.

^e 6-Morpholino is less deactivating (10⁶ *k* = 156) and 6-dimethylamino (10⁶ *k* = 54) and more deactivating than 6-anilino (10⁶ *k* = 324).

^f Values are for 6-methylamino and 6-dimethylamino compounds; for 6-anilino, *E*_A is 12.0 and Δ*S*[‡] is –39.

^g Rate increased with the percent of reaction due to catalysis by the anilino-*s*-triazine produced.

TABLE VII
NITROPYRIDINES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTION

Line No.	Pyridine substituents	Nucleophile in 99.8% EtOH ^a	Rate constant ^b (temp. °C) 10 ⁶ <i>k</i> liter mole ⁻¹ sec ⁻¹	Activation energy ^c kcal mole ⁻¹	Frequency factor ^d log ₁₀ A	Ref.
1	2-Cl-3-NO ₂	piperidine	(30°) 4.19 × 10 ³	12.0	6.2	167
2	2-Cl-3-NO ₂	pyridine	(55°) 1.03	18.7	6.3	404
3	2-Cl-3-NO ₂	3-picoline	(55°) 1.81	18.5	6.6	404
4	2-Cl-3-NO ₂	4-picoline	(55°) 3.15	17.4	6.1	404
5	2-Cl-3-NO ₂	<i>m</i> -toluidine	(55°) 22.4	14.4	5.0	404
6	2-Cl-3-NO ₂	<i>p</i> -toluidine	(55°) 50.0	13.9	4.9	403
7	2-Cl-3-NO ₂	aniline	(55°) 16.9	14.5	5.0	403
8	2-Cl-5-NO ₂	piperidine	(30°) 6.7 × 10 ³	11.5	6.1	167
9	2-Cl-5-NO ₂	pyridine	(55°) 1.97	18.1	6.3	404
10	2-Cl-5-NO ₂	3-picoline	(55°) 4.00	17.9	6.6	404
11	2-Cl-5-NO ₂	4-picoline	(55°) 6.11	17.5	6.5	404
12	2-Cl-5-NO ₂	<i>m</i> -toluidine	(55°) 15.8	12.9	3.8	404
13	2-Cl-5-NO ₂	<i>p</i> -toluidine	(55°) 34.3	12.7	3.9	403
14	2-Cl-5-NO ₂	<i>p</i> -anisidine	(55°) 1.01 × 10 ²	11.5	3.5	403
15	2-Cl-5-NO ₂	aniline	(55°) 11.9	13.1	3.8	403
16	2-Cl-5-NO ₂ -4-Me	piperidine	(30°) 1.26 × 10 ³	12.4	6.0	167
17	4-Cl-3-NO ₂	pyridine	(55°) 32.1	16.9	6.8	404
18	4-Cl-3-NO ₂	3-picoline	(55°) 39.8	15.6	6.0	404
19	4-Cl-3-NO ₂	4-picoline	(55°) 66.4	15.1	5.8	404
20	2-Cl-5-NO ₂	aniline (MeOH)	(40°) 4.90	14.9 ^e	5.1	489b
21	2-Cl-5-NO ₂ -5-CN	aniline (MeOH)	(30°) 1.1 × 10 ⁴	9.8 ^e	5.2	489b

^a Water was added to absolute ethanol to make 99.8% ethanol.

^b Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperature given in parentheses.

^c The Arrhenius activation energy,⁴⁷⁹ E_A.

^d The Arrhenius frequency factor,⁴⁷⁹ A, is in units of liter mole⁻¹ sec⁻¹.

^e Values of ΔH[‡] were also given.

TABLE VIII
NITROBENZENES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTION

Line No.	Benzene substituents	Nucleophile	Solvent	Rate constant ^a (temp. °C) 10 ⁶ <i>k</i> liter mole ⁻¹ sec ⁻¹	Energy of activation ^b kcal mole ⁻¹	Frequency factor ^c log ₁₀ A	Ref.
1	2-Cl-1-NO ₂	MeO ⁻	MeOH ^d	(90°) 1.50 × 10 ²	23.5	10.3	488
2	2-Cl-1-NO ₂	EtO ⁻	EtOH ^e	(90°) 3.97 × 10 ²	22.2	10.0	73
3	2-Cl-1-NO ₂	piperidine	benzene	(90°) 54	13.4	3.8	73
4	2-Cl-1-NO ₂	piperidine	EtOH	(90°) 29.8	18.1	6.4	73
5	4-Cl-1-NO ₂	EtO ⁻	EtOH	(90°) 9.63 × 10 ²	20.1	9.0	73
6	4-Cl-1-NO ₂	piperidine	benzene	(90°) 1.1	13.7	2.3	73
7	4-Cl-1-NO ₂	piperidine	EtOH	(90°) 10.8	17.1	5.3	73
8	4-F-1-NO ₂	EtO ⁻	EtOH	(90°) 2.2 × 10 ⁵	19.0	10.7	73
9	4-F-1-NO ₂	piperidine	EtOH	(90°) 2.25 × 10 ³	13.2	5.3	73
10	4-Cl-1,3-(NO ₂) ₂	MeO ⁻	MeOH ^d	(20°) 1.8 × 10 ⁵	17.4	11.3	53
11	4-Cl-1,3-(NO ₂) ₂	pyridine	EtOH ^e	(55°) 11.1	16.7	6.2	404
12	4-Cl-1,3-(NO ₂) ₂	3-picoline	EtOH ^e	(55°) 19.9	17.1	6.7	404
13	4-Cl-1,3-(NO ₂) ₂	4-picoline	EtOH ^e	(55°) 30.9	16.9	6.7	404
14	4-Cl-1,3-(NO ₂) ₂	aniline	EtOH ^e	(55°) 3.53 × 10 ²	11.2	4.0	403
15	4-Cl-1,3-(NO ₂) ₂	<i>p</i> -toluidine	EtOH ^e	(55°) 9.70 × 10 ²	10.1	3.6	403
16	4-Cl-1,3-(NO ₂) ₂	<i>p</i> -anisidine	EtOH ^e	(55°) 2.96 × 10 ³	9.7	3.9	403
17	4-Cl-1,3-(NO ₂) ₂	piperidine	EtOH ^e	(30°) 3.09 × 10 ⁴	10.7	6.2	488
18	4-Cl-1,3-(NO ₂) ₂ -6-Me	piperidine	EtOH ^e	(30°) 8.7 × 10 ³	11.6	6.3	488
19	2-Cl-1,3-(NO ₂) ₂	piperidine	EtOH ^e	—	12.2	5.9	167

^a Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperature given in parentheses.

^b The Arrhenius activation energy,⁴⁷⁹ E_A.

^c The Arrhenius frequency factor,⁴⁷⁹ A, is in units of liter mole⁻¹ sec⁻¹.

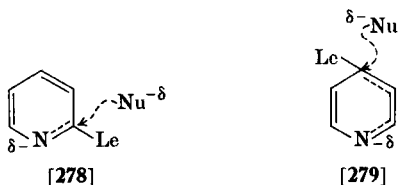
^d Absolute methanol.

^e Water was added to absolute ethanol to make 99.8% ethanol.

Usually, only the Arrhenius energy of activation, $^{479}E_A$, is given in these papers; it differs from the heat of activation, $^{481}\Delta H^\ddagger$, by RT (about 0.6 kcal at ordinary temperatures). Only a few entropies of activation, $^{482}\Delta S^\ddagger$, were calculated; the frequency factor, 479 whose logarithm is tabulated, is proportional to this reaction parameter. It is clear that the rate, E_A , ΔH^\ddagger , and ΔS^\ddagger determined for an S_NAr2 reaction are for the overall, two-stage process. Both stages will contribute to the overall results when their free energies of activation 482 are similar.

Chapman and his co-workers 55,73,404 have concluded that the reversibility of several of these reactions is not significant enough to be included in the kinetic considerations. Radioactive isotopes could be used to measure the degree of reversibility, even if very low, and kinetic parameters on the reverse substitution process could also be obtained.

The activation energy of substitution of an unactivated aromatic halide (e.g., fluorobenzene 74 and 2-chloronaphthalene 55,139) is over 30 kcal while that of activated compounds is 5–20 kcal. For the tabulated reactions (Tables II–VIII) with alkoxide and with primary, secondary, or tertiary amines, resonance activation (cf. **278** and **279**) by *ortho* or *para* nitrogens is found to be greater than inductive activation (cf. **251**). This relation is qualitatively demonstrated in

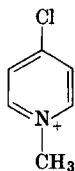


Section III, B and quantitatively supported in this section for azines (pyrazine, Table IV, line 1 vs. pyrimidine, Table III, line 4), for azinium compounds (pyridinium derivatives, Table II, lines 5–10, and pyridazinium compounds 235) and for nitropyridines (Table VII). Comparison of the reaction 487 of piperidine with 2-chloropyrazine (**270**) and 2-chloropyrimidine (**266**) (E_A 11.5 kcal) reveals a greater than 200-fold acceleration due to shifting the azine-nitrogen from inductive to resonance action. The *ortho* and *para* resonance activation results in a considerably greater decrease in the energy of activation than that produced by *meta* inductive activation. The greater rate of reaction associated with both types of activation is primarily due to lowering of the activation energies. Inductive activation is clearly

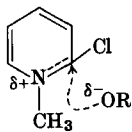
evident in the qualitative comparisons of halo-pyridazines or -pyrazines vs. halopyridines (Section III, B), in the activation energies of piperidino-dechlorination⁴⁸⁷ of 2-chloropyridine (**272**) (E_A 17.1 kcal) and of 2-chloropyrazine (**270**) (E_A 13.2 kcal), and in the high reactivity of 3-chloropyridine 1-oxide (Table II line 16 vs. line 12).

In the absence of the specific effects already discussed, the activation by azine-nitrogen is greater from the *para* than from the *ortho*-position. For example, 4-chloropyridine (**271**) reacts with ethoxide ion 40 times as fast as 2-chloropyridine (**272**) due to a lower (by 6 kcal) activation energy (Table II, lines 1 and 4). A similar difference is observed with methoxide ion (Table II, lines 11 and 13). Comparison of 4-chloropyrimidine (**264**) with the 2-isomer (**266**) (Table III, lines 2 and 10) and of the related *C*-methyl analogs (Table III, lines 6, 7, and 11–14) in their reactions with piperidine or morpholine shows a difference in E_A of about 2 kcal. The ratio of rates is about 10 (11 using the 2-methyl derivative, Table III, lines 11, 12; 8 using the 6-methyl compound, Table III, lines 13 and 14). The transition state for amination of 2-chloropyrimidine has the reagent's partly cationic nitrogen near two partly anionic azine-nitrogens while that for amination of the 4-isomer has only one nearby anionic azine-nitrogen. The additional electrostatic attraction possible in the former is not sufficient to overcome the difference in activation.

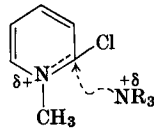
The general principle that *activation* of *para* substitution is greater than of *ortho* substitution holds true also for an azinium moiety in the one instance studied. Thus, the activation energy for the 4-chloropyridine quaternary salt **280** (Table II, line 9) is 1 kcal lower than that for the 2-isomer (line 5). The rate relation (2- > 4-isomer) is controlled by the entropies of activation in this reaction due to electrostatic attraction in the transition state (**281**). The reverse rate relation (4- > 2-position) is predicted for aminations of such quaternary compounds due to electrostatic repulsion (**282**) plus the difference in E_A . A kinetic study of the 2- and 4-pyridine quaternary salts



[280]



[281]



[282]

(Table II) using ethoxide ion is needed to show the relation of the kinetic parameters for cationized and uncharged azine-nitrogen. The greater activation resulting from conversion of an azine-nitrogen into an azinium moiety (Table II) has been estimated^{486b} from the available data to be 10^8 – 10^{13} -fold (rate constant), depending on the ring-position.

The reactivity of the chloropyridine *N*-oxides with methoxide ion (Table II, lines 14, 16 and 18) also supports the general principle of *para* > *ortho* activation. With piperidine, 2-chloropyridine *N*-oxide reacts at a somewhat greater rate than the 4-isomer, probably due to a cyclic transition state involving hydrogen bonding of the reagent to the anionic *N*-oxide oxygen (possibly through a cyclic solvate analogous to **235**) rather than due to electrostatic attraction (cf. ref. 97c which shows latter is not significant in nitrobenzene derivatives).

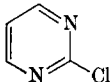
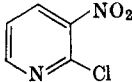
Activation in terms of E_A is in the order 4- > 2- \gg 3-position for the methoxy-dechlorination^{486b} of chloro-pyridines, -pyridine *N*-oxides, and -pyridine quaternary salts (Table II). In methoxylation^{486b} and piperidination^{486b} of the 2-, 3- and 4-chloro derivatives of pyridine, nitrobenzene (Table VIII), pyridine *N*-oxide, and 1-methylpyridinium cation, the activation in terms of E_A is in the order benzene C—H < pyridine N < benzene C—NO₂ < pyridine $\overset{+}{N}$ —O[−] < pyridine $\overset{+}{N}$ —CH₃ for these activating centers. The same relationship quinoline ring-*N* < naphthalene C—NO₂ < quinoline *N*-oxide holds for the 4-halo bicyclic compounds in Table XI and for fluoro-quinolines and -pyridines.^{255b}

The Arrhenius parameters and rate constants for methoxylation¹⁰³ of halonitrobenzenes are (E_A , ΔS^\ddagger , and 10^6k given): 2-chloro (22.8, −13.4, 103 at 85°) and 4-chloro (23.1, −10.1, 385 at 85°); for piperidination^{73, 486d} in 99.8% ethanol (E_A , $\log_{10}A$, ΔS^\ddagger , and 10^6k given): 2-chloro (18.1, 6.4, −32, 14.4–14.7 at 80°) and 4-chloro (17.1–17.7, 5.3–5.8, −37, 5.55–6.14 at 80°).

The effect of replacing an adjacent ring-carbon with a ring-nitrogen is a large decrease in the activation energy (7.5–10 kcal) and a large increase in the rate (700,000-fold) as observed for reactions of ethoxide ion or piperidine with 2-chloropyridine (**272**) (Table II, lines 1 and 2) and 2-chloropyrimidine (**266**) (Table III, lines 1 and 2). Replacing a ring-carbon opposite the leaving group produces an additional 2 kcal decrease in E_A and the further 10-fold acceleration noted for 4-chloropyrimidine (**264**) (Table III, line 10). The insertion of a *para* azine-nitrogen into 2-nitrochlorobenzene to form 4-chloro-3-

nitropyridine (**289**) produces a decrease in the activation energy of about 9 kcal for reaction with ammonia.^{489a} Insertion of an *ortho* azine-nitrogen into 4-nitrochlorobenzene to form 2-chloro-5-nitropyridine (**290**) produces a 5.6 kcal decrease in E_A and a 600-fold acceleration of piperidino-dechlorination. In the uncatalyzed reaction of aniline with 2,4,6-trichloropyrimidine (Table V, line 6) and 2,4,6-trichloro-*s*-triazine (Table VI, line 1), there is a 200,000-fold acceleration due to the additional ring-nitrogen. The large increase in the reactivity produced by additional ring-nitrogens is also quite apparent from the qualitative indications of preparative organic chemistry cited in Section III, B.

Greater charge dispersal in the transition state may cause a greater rate of ethoxy-dechlorination for nitrohalobenzenes (**38** and **39**) than for chloropyridines (**40** and **41**) as discussed in Sections II, B, 1, a and II, E, 2, c. The kinetic parameters are given in Table VIII, lines 2 and 5, and in Table II, lines 1 and 4.

			
$k \times 10^4 (30^\circ)$	6.7	41.9	} Nu = piperidine
E_A	12.4	12.0	
$\log_{10} A$	5.7	6.2	
	[283]	[284]	

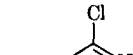

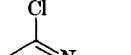
The relation of the activating effects of an azine-nitrogen and a nitro group depends on the compounds chosen for comparison and on the nucleophile. The ratio of the rates of reaction of **283** (Table III, line 2) and of **284** (Table VII, line 1) is

$$\frac{\textit{ortho azine-N}}{\textit{ortho NO}_2} = \frac{1}{6}$$

The rate ratio for piperidino-dechlorination of **285** (Table III, line 13), of **286** (Table VII, line 16), and of **287** (Table III, line 11) involves comparison of the activations from the *para*-position. The ratios for the two comparisons, **285** vs. **286** and **287** vs. **286**, are

$$\frac{\textit{para azine-N}}{\textit{para NO}_2} = \text{ca. } 2$$

The special effect of an *ortho*-nitro group, noted by Chapman *et al.*⁴⁰³ in reactions with primary or secondary amines but not with tertiary

			
$k \times 10^3 (30^\circ)$	2.14	1.26	3.0
E_A	11.0	12.4	10.6
$\log_{10} A$	5.2	6.0	5.1
[285]	[286]	[287]	Nu = piperidine

bases,^{97f} is involved in the comparison of effects in the *ortho*-position (cf. **284** vs. **283**) given above. A comparison free from this effect (requires NH to be present in the transition state and intermediate complex) is available from nucleophilic substitution of **288–291** by pyridine. The relationship of the entropies of activation (proportional

$k \times 10^6 (55^\circ)$	11.1	32.1	1.97	1.03
E_A	16.7	16.9	18.1	18.7
$\log_{10} A$	6.2	6.8	6.3	6.3
[288]	[289]	[290]	[291]	Nu = pyridine

to $\log_{10} A$) seems primarily responsible for the greater reaction rate of the azine **289** than of the nitro analog **288**:

$$\frac{\text{para azine-N}}{\text{para NO}_2} = 3$$

In the comparison of **285**, **286**, and **287** the lower energy of activation for the *para* azine-nitrogen compounds **285** and **287** was responsible for their more rapid reaction. Both ratios of rates are about the same, the reactivity being greater for the azine-nitrogen compound in each case. Another relationship of moieties in the *ortho*-position is derived from comparison of **290** and **288**, the rate difference being entirely due to the relationship of the activation energies. This ratio is essentially the same as that for **283** and **284**, which involved both the entropy and

entropy of activation differences. The often-repeated generalization "a *para* heterocyclic nitrogen approximates a *para* nitro group in activating effect while an *ortho* ring-nitrogen is definitely less effective than an *ortho* nitro group" is based on the semi-quantitative work of Mangini *et al.*^{339, 414} A much more valid comparison has been provided by the work of Chapman *et al.* cited above. However, further work with other nucleophiles and with variation of the hydrogen-bonding character of the solvent would be desirable.

Chapman *et al.*⁴⁰³ have commented on this "fundamental difference between nitro groups and cyclic [azine] nitrogen atoms." The difference is in the effect produced by shifting the activating center from the *para*- to the *ortho*-position: for a NO₂ group, the shift **290** to **291** causes only a small (2-fold) decrease in the rate due to a slight increase in E_A ; for an azine-N, the shift **289** to **291** brings about a large (32-fold) decrease in the rate due to a larger increase (2 kcal) in E_A coupled with an entropy effect acting in the same direction.

An interesting but complex comparison is provided by **289** and **290** where the positions of the nitro and azine-nitrogen moieties are interchanged. The rate ratio of **289**:**290** is 16, and the ratio arises because the entropy and energy of activation differences act in the same direction. This relationship demonstrates that the purely electrostatic effect (attraction between partly cationic nucleophile-nitrogen and partly anionic azine-nitrogen in the transition state from **290**) is not predominant here since the opposite charges in the transition state (anionic centers are oxygens of the nitro group, in this case) from **289** are farther apart (cf. Section I, D, 2, b).

The rate of reaction of a series of nucleophiles with a single substrate is related to the basicity when the nucleophilic atom is the same *and* the nucleophiles are closely related in chemical type. Thus, although the rates parallel the basicities of anilines (Tables VII and VIII) as a class and of pyridine bases (Tables VII and VIII) as a class, the less basic anilines are much more reactive. This difference in reactivity is based on a lower energy of activation as is the reactivity sequence piperidine > ammonia > aniline. Further relationships among the nucleophiles found in this work are: morpholine vs. piperidine (Table III); methoxide vs. 4-nitrophenoxide (Table II); and alkoxides vs. piperidine (Tables II, III, and VIII). Hydrogen bonding in the transition state and acid catalysis increase the rates of reaction of anilines. Reaction rates of the pyridine bases are decreased by steric hindrance between their *alpha* hydrogens and the substituents or

hydrogens adjacent to the leaving group.^{403,404} Many comparisons of nucleophiles involve not only nucleophilicity but also strong variation in the energies of hydrogen-bonding solvation of reagents (hydrogen bonding to *Nu* will increase with basicity) and transition states, in addition to the more general effect of the dielectric constant of the solvent.

The effect of the leaving group is illustrated in the comparison of fluoro- and chloro-nitrobenzenes (Table VIII) in their reactions with ethoxide ion (lines 5 and 8) and with piperidine (lines 7 and 9). Rate ratios F:Cl are 23:1 (opposing E_A and entropy of activation changes) and 201:1 (E_A effect), respectively, for the two nucleophiles. For the reasons discussed in Section II, D, 1, a fluorine substituent produces a lower energy of repulsion of the nucleophile and thus facilitates reaction.

The catalytic effect of protons, of bifunctional catalysts, and of base is demonstrated^{218,475} in the amination of chloro derivatives of pyridazine, pyrimidine, and *s*-triazine (Tables V and VI). Anilino-*s*-triazines containing NH groups act as catalysts in their own formation.^{382,475} The catalytic action of protons on anilino-dechlorination of 2-chloro-4,6-diamino-*s*-triazine and of 2-amino-4-chloropyrimidine was reported in the classic paper by Banks.²⁴⁴

The effect of the entropy of activation was noted above for the quaternary pyridine salts (**280** and **281**). In future work, it may also be found to reflect the electrostatic or hydrogen-bonding interactions in transition states of amination reactions and the effect of reversible cationization of an azine-nitrogen. Brower *et al.*⁴⁸⁷ observed a substantial rate difference between piperidino-dechlorinations of 2-chloropyrimidine in petroleum ether and in alcohol due partly to the higher entropy of activation in the latter solvent (Table III, lines 3 and 4).

The effect of activating and deactivating substituents is illustrated by the following: 7,000-fold acceleration by a cyano group (Table VII, line 21); 2–5-fold deceleration by an alkyl group in chloropyrimidines (Table III, lines 2 and 5–9) and in nitrochloropyridines (Table VII, lines 8 and 16); 12–18-fold acceleration by a 6-chloro group in 2,4-dichloro- vs. 2,4,6-trichloro-pyrimidine (Table V); cf. 6-alkoxy, 6-alkylthio and 6-substituted-amino groups in 4-anilino-2-chloro- and 2,4-dichloro-*s*-triazines^{377,490a} (Table VI); and 2-substituents (H, Me, furyl, phenyl) in 4-chloro-6-methylpyrimidines with alkoxides or amines.^{490b}

B. MONOCYCLIC AZINES. BEHAVIOR OF SIMPLE DERIVATIVES WITH NUCLEOPHILES

1. General Aspects

These ring systems are taken up in order of increasing number of ring-nitrogens, and the poly-azines are arranged according to the numbering of the azine-nitrogens (1,2; 1,3; ... 1,2,3; 1,2,4; 1,3,5; etc.).

Statements in the literature on the reactivity of the ring-positions in monocyclic azines are conflicting. Reactivity is said to be greater at the position *ortho* (or *alpha*) than at the position *para* (or *gamma*) to an azine nitrogen: 2- > 4-position in pyridine⁴⁹¹ and pyrimidine^{492,493} and 3- > 5-position in *as*-triazine.⁴⁹² By others, the reactivity has also been considered equal in pyridine^{129a,d, 494} and in pyrimidine.^{129a, d, 495} In contrast, greater reactivity *para* to the ring-nitrogen was considered generally true for pyridines^{136b, 496} and pyrimidines⁴⁹⁷ and is supported by Chapman and his associates' work^{55, 167, 404} on pyridines and pyrimidines (Section III, A, 2). The sources of the difficulty in arriving at a valid generalization are (a) giving too much weight to the electron deficiency (Section I, B, 2) in the ground state which leads to the *expectation* of greater reactivity at the positions adjacent to a ring-nitrogen, and (b) including diverse kinds of poly-substituted azines (Section II, E,) and several different reaction types (Sections II, B and III, A). The characteristics of these types can produce a moderate change in the ratio of the reaction rates (cf. amination vs. alkoxylation of chloroazines cited in Section III, B) or a large change (as in reaction of *N*-methyl quaternary derivatives¹³¹ of chloropyridines, Table II, p. 270). Alteration of the relative reactivity of ring-positions by the following is discussed in the sections indicated: hydrogen bonding in Sections II, B, 3 and II, C; cationization of an azine-nitrogen in Section II, C; cyclic transition states and intramolecular substitutions in Sections II, B, 5 and II, F; the leaving group in Section II, D; and other nuclear substituents in Section II, E. The significance of the hydrogen bonding of a reagent to an azine-nitrogen is indicated in Sections III, B, 2, III, B, 3, a, and III, B, 3, b and of the hydrogen bonding of the solvent (especially water) to an azine-nitrogen in these same sections. The extent of either kind of hydrogen bonding will vary with the position of the substituent, e.g., 4-chloro- > 2-chloro-pyridine.

Yield data can be used to deduce the relative reactivity only when much is known about the reactions to be compared (discussed in

detail by Bunnett⁴⁹⁸). The reactions must be incomplete ($> 10\%$ but $< 90\%$), not reversible, and without appreciable side-reactions or further reactions of the products (the more reactive site is usually associated with the more reactive product). The series of reactions must also have been carried out under the same conditions, in the same solvent, and then the isolation performed *efficiently* and in the same way. Usually not all this is known about organic preparations and isolated yields are determined largely by practical considerations. Yields are included in this section to indicate the validity or weakness of conclusions about relative reactivity or selectivity.^{477b}

2. Monoazine (Pyridine)

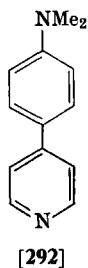
The reactivity of 2- and 4-halopyridines toward a variety of nucleophiles is far greater than that of the 3-halo isomers (**274**), which are nevertheless appreciably activated. The 4-position (cf. **271**) is more reactive than the 2-position (cf. **272**), except when the specific factors described in Sections II, B and III, A and also below, produce an increase in the reactivity at the 2-position. Pyridine derivatives are the least reactive of the monocyclic azines (cf. Scheme I, p. 266).

In reaction with ethoxide ion, Chapman and Russel-Hill⁵⁵ have established that the chloro group in 4-chloropyridine is displaced 3 times as rapidly at 120° as that in 2-chloropyridine and 40 times as rapidly at 20° . Conclusions based on the relative reactivity of polyhalopyridines (and other azines) must be regarded as very tentative. Halogens produce an appreciable activation of each other (cf. Sections II, E and III, A, 2), and it is not sufficiently appreciated that this *mutual activation is generally not equal*. 2,4-Dichloropyridine has been di- but not mono-alkoxylated.²⁵⁷ Its 2,4,6-tribromo analog on boiling for 2 hr in dilute methanolic sodium *hydroxide* gave the 4-methoxylation product^{477b} and on longer heating only 2,4-dimethoxy-6-bromopyridine (quantitative yield) was formed.¹⁸³

The reaction of 2,4,6-tribromopyridine with phenoxide ion¹⁸² illustrates, in our opinion, the effect of hydrogen bonding as discussed in Section II, B, 3. Reaction (150° , 24 hr) in water gave approximately equal amounts (18% yields) of 2- and 4-monosubstitution, but in phenol under the same conditions only^{477b} the 2-phenoxy derivative (in high yield plus a small amount of the 2,6-diphenoxy compound) was formed. In water, reaction at the adjacent 2- and 6-position is hindered by the hydrogen bonding (cf. **61**) of the *solvent* to the azine-nitrogen, compared to reaction at the 4-position. On the other hand, in

phenol the conjugate acid of the *nucleophile* is hydrogen-bonded to the azine-nitrogen thus favoring reaction at the adjacent 2- or 6-positions. The effect of partial cationization of the azine and factors involved in acid-catalyzed reactions adjacent to protonated ring-nitrogens are discussed in Section II, B, 3.

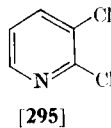
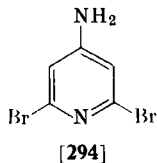
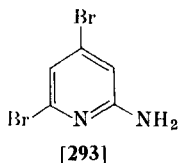
The directive effect of the electrostatic factor in acid catalysis seems clear from the large change in the 4- vs. 2-position reaction rates on cationization (cf. **280** and **281**) of the chloropyridines (Table II, p. 270) by *N*-methylation. The 2-isomer at 55° reacts 30 times as fast as the 4-isomer with 4-nitrophenoxide ion, and the electrostatic nature of the effect is evident from the relation of the entropies and energies of activation. It would be very interesting to study amination of such cationic substrates to see if the rate ratio is reversed. The quaternization produces a large increase in the rate which has been approximated (10^8 – 10^{13} -fold).^{486b} The high reactivity of quaternary pyridine salts is evident from the substitution by iodide ion which occurs on attempted preparation of iodide salts of 2-chloropyridinium compounds²³⁰ and from the nucleophilic substitution (replacement of hydrogen) of 1-benzoylpyridinium ion by the benzene π -electrons of *N,N*-dimethylaniline to give **292**⁴⁷² with loss of the 1-benzoyl group as benzaldehyde.



4-Halopyridines undergo self-quaternization^{412,499} on standing while the less reactive 2-halo isomers do not. However, more is involved here than the relative reactivity at the ring-positions. The reaction rate will depend on the relative nucleophilicity of the attacking pyridine-nitrogens (4-chloropyridine is more basic) and on the much lower steric hindrance at the 4-position. Related to this self-quaternization are the reactions of pyridine and picolines as nucleophiles with 4-chloro- and 2-chloro-3-nitropyridines. The 4-isomer (**289**) is again the more reactive by 10–30-fold (Table VII, p. 276).

The kinetic comparison of amination of the chloropyridines is incomplete due to the intervention of acid catalysis. The reaction of 2-chloropyridine with piperidine shows a constant rate coefficient as the reaction proceeds to completion, but, with the less basic morpholine, a rising coefficient indicative of acid catalysis is observed.⁵⁵ 4-Chloropyridine exhibits a rising rate coefficient even with piperidine.⁵⁵

The relative displacements of halogen in polyhalopyridines indicates the operation, in amination reactions, of hydrogen bonding of the solvent and of the reagent (in aprotic solvents) to an azine-nitrogen in the ground state and of the effects shown in **276** and **277** in the transition state. Reaction (160°, 3 hr) of 2,4,6-tribromopyridine with concentrated aqueous ammonia gave 30% yields of both the 2-amino-4,6-dibromo and 4-amino-2,6-dibromo derivatives.⁵⁰⁰ The trichloro analog behaves similarly.⁵⁰¹ Here, a transition state such as **235** is suggested since hydrogen bonding to the pyridine-nitrogen by ammonia should be very much less than that by water. The rate of the



predominant 4-amination of 2,4,6-tribromopyridine in dilute aqueous ammonia is higher than that of the major 2-amination in *n*-butanol.^{184a} This acceleration is very likely due to the partial cationization (Section II, C) produced by hydrogen bonding; the hydrogen-bonding ability and not the polarity^{184a, 501} of the solvent is important. In *n*-butanol, the reagent is appreciably hydrogen-bonded to the adjacent ring-nitrogen, while in aqueous solution only solvent is hydrogen-bonded and reaction at the 2-position is hindered (cf. **61**). The products from 2,4,6-tribromopyridine using a longer reaction time (6% aqueous ammonia, 160°, 8 hr) were: 35% of 2-amino-4,6-dibromo- (**293**) and 35–40% of 4-amino-2,6-dibromo-pyridine (**294**) plus the mixed diamines. The results in *n*-butanol (3.5% ammonia gas) were: 55–56% of 2-amino-4,6-dibromo- and 15–20% of 4-amino-2,6-dibromo-pyridine plus 10% of the mixed diamines. The earlier report⁵⁰² on amination of this substrate is misleading in that only a *very low yield* of one product was isolated.^{477b}

An extensive study of the amination of halopyridines has been carried out by den Hertog and co-workers.^{501, 503} A comparison of their results with studies in inert solvents using primary and tertiary amines should permit some evaluation of the postulated factors. 2,4-Dichloropyridine in concentrated aqueous ammonia (180°, 5 hr) resulted in the formation of 4-amino- (60% yield) and 2-amino-chloropyridines (20% yield).⁵⁰³ Under similar conditions, only 4-substitution of 3,4,6-trichloro- and of 2,3,4,5-tetrabromo- and -tetrachloro-pyridines was observed.^{477b} However, in these and the other polyhalo pyridines, the appreciable and unequal mutual activation by the halogen substituents needs to be emphasized.

The inferior activation in the 3- or *beta*-position is illustrated by the very large difference in reactivity in the following aminations and alkoxylation. In the reaction of 2-chloro-5-iodopyridine or 2,3-dibromopyridine (cf. **295**) with boiling methanolic methoxide, only the 2-halogen is displaced^{504, 505} as is also the case in the amination of 2-chloro-3,5-diiodopyridine¹³⁸ and of 2,3,6-tribromopyridine.⁵⁰⁰ 4-Amination of 3,4-dibromo-, 2,3,4,5-tetrabromo-, and 3-bromo-4-chloro-pyridine occurred.⁵⁰⁶ Only 2-amination (aqueous NH₃, 190°, 36 hr) occurred with 2,3-dichloropyridine (**295**) and only 4-ethoxylation (alcoholic ethoxide, 160°, 4 hr) with 3,4-dichloropyridine.⁵⁰¹

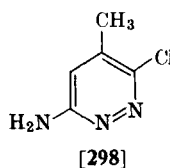
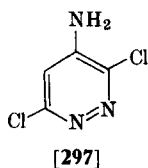
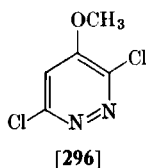
Reactions of 3-substituted pyridines (**274**) are appreciably facilitated by charge stabilization in the transition state, even though by only the inductive effect of the ring-nitrogen (cf. **251**). Methanolic methoxide reacts with 3-bromopyridine (150°, 48 hr)⁵⁰⁷ and 3,5-dibromopyridine⁵⁰⁸ (105°, 18 hr) to give good yields of the monomethoxy derivatives. On heating (200°, 5 hr) 3,5-dichloropyridine with ethanolic sodium ethoxide, disubstitution occurs.⁵⁰⁹ The considerable activation by the ring-nitrogen is evident since reaction of bromobenzene with sodium methoxide requires a temperature of 250°. ⁵⁰⁷ 3-Bromopyridine is also definitely more reactive toward ammonia and amines^{510a} and has a lower activation energy^{510b} than bromobenzene in reacting with piperidine. Substitution (110°, 1 hr) with phenylacetonitrile carbanion⁵¹¹ denotes a significant activation.

Nucleophilic substitution of pyridines is discussed in previous sections in relation to the following: cyclic transition states (Section II, B, 5), hydrogen bonding and cationization (Section II, C), the leaving group (Section II, D,) and the effect of other substituents (Section II, E) and of the nucleophile (Section II, F).

3. Diazines

a. *Pyridazine*. There are two different kinds of ring-positions in pyridazine, the 4-(or 5-)position being more susceptible to nucleophilic attack than the 3-(or 6-)position (cf. **269**). Reactions of 3-chloro-,⁵¹² 4-chloro-, 3,4-dichloro-, 3,5-dichloro-, and 4,5-dichloropyridazines with alkoxides are not known. No kinetic comparisons of pyridazine derivatives are available so one must rely on qualitative indications derived from preparative organic chemistry. There is clear justification for ranking 3- or 4-pyridazinyl derivatives (**269** or **268**) as more reactive than 2- or 4-pyridyl derivatives (**272** or **271**) and as less reactive than 2- or 4-pyrimidinyl compounds (**266** or **264**). Reactivity factors other than activation by ring-nitrogens are referred to in Section III, B, 1 and are illustrated herein.

The ease of reaction of halopyridazines is indicated by the exothermic nature of the reaction of 3,6-dichloropyridazine^{320, 425} with sodium methoxide at room temperature to yield 3-chloro-6-methoxypyridazine. Displacement of the deactivated chloro group in the latter required heating (65°; < 8 hr) the reaction mixture. Competitive methoxy-dechlorination (20°, 12 hr) of 3,4,6-trichloropyridazine shows the superior reactivity of the 4-position; the 3,6-dichloro-4-methoxy analog^{513a} (**296**) was isolated in high yield. The greater reactivity of the



4-position is also shown by the fact that the sulfanilamide anion selectively^{477b} displaces the poorer leaving group, the methoxy group, from 3,6-dichloro-4-methoxypyridazine.^{399a} The 4-positions of 3,4,6- and 3,4,5-trichloropyridazine are more reactive^{434b, 464, 513b} than the 3- or 6-positions toward alkoxide, hydroxide or thiocyanate ions, ammonia, hydrazine, or sulfanilamide anion. In the amination (alcoholic NH₃, 120°, 5 hr) of 3,4,5-trichloropyridazine, products of displacement at both positions *para* to a ring-nitrogen were formed in about equal amounts.^{434b, 514a} Similar amination of 3,4,6-trichloropyridazine gave the 4-amination product (**297**) which was isolated in 30% yield.^{514b}

In contrast to the greater reactivity at the 4-position with the nucleophiles mentioned above, both 3,4,6- and 3,4,5-trichloropyridazine react with glacial acetic acid to give dichloro-3(2*H*)-pyridazinones⁴⁶⁴ via substitution catalyzed by the liberated hydrochloric acid or the acetic acid solvent. The selectivity is attributed in Section II, F to a cyclic transition state such as **238** involving attack by a bifunctional nucleophile, either acetic acid or acetate ion. The position of reaction of 3,6-dichloro-4-methylpyridazine with various nucleophiles is solvent-dependent. Hydrogen bonding of the solvent (steric hindrance at the 6-position favors reaction at the 3-position) or of the reagent (favors reaction at the 6-position) at the more basic 1-nitrogen was postulated (Section II, E, 2, a, **162**) as the basis for this behavior. Generally, a mixture of products is obtained; for example, with methanolic ammonia, a mixture of 80% of 6-amino-3-chloro-4-methyl (**298**) and 10% of 3-amino-6-chloro-4-methyl derivatives is obtained.^{361a, 362} However, in the more strongly hydrogen-bonding solvent, water, a mixture of 50% and 40%, respectively, of these two isomers is obtained (cf. ref. 292d).

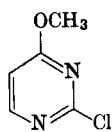
In earlier sections, the effects of the following on nucleophilic substitution of pyridazines are described: hydrogen bonding and cationization (Section II, C), the leaving group (Section II, D), other nuclear substituents (Section II, E), and the nucleophile (Section II, F).

b. *Pyrimidine*. The relative order of displaceability in the halopyrimidines is 4- > 2- \gg 5-position, subject to the intervention of the specific effects mentioned in Section III, B, 1. From work on pyrimidine derivatives, we have proposed¹⁵³ that maximal dispersal of the negative charge in space in the transition state is one factor in determining its free energy. The only kinetic comparison¹⁶⁷ of pyrimidines demonstrates that 4-chloropyrimidine (**264**) is more reactive than the 2-isomer (**266**) toward secondary amines. Qualitative and semi-quantitative indications from preparative organic chemistry support this reactivity relationship. From such indications and from kinetic studies, 2- or 4-pyrimidinyl compounds appear to be more reactive than 2-pyrazinyl (**270**) and 2- or 4-pyridyl compounds (Tables II-IV, pp. 270-273) and less reactive than 2-*s*-triazinyl derivatives (**258**) (Tables V and VI, pp. 274 and 275).

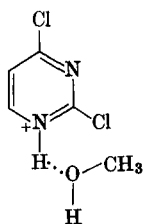
Although pyrimidine chemistry covers 145 years, many of the simplest derivatives have only recently been made, as illustrated by the recent preparation⁴⁷⁴ of 5-bromopyrimidine (**273**). This compound

has good reactivity toward alcoholic methoxide (substantial at 65°; 70% at 100°, < 16 hr) and ethanolic ethyl mercaptide (78°, 2 hr, 60% yield). Kinetic study of this compound and its chloro analog⁵¹⁵ will permit one to relate 5-pyrimidinyl activation to that in pyridine and pyrazine.

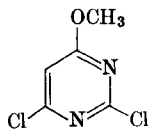
The 2- and 4-chloro derivatives readily react with sodium methoxide in methanol at reflux (and probably at 25°) to yield 2-methoxy-⁵¹⁶ and 4-methoxy-pyrimidine.³²⁶ The high order of reactivity of the 4-position is evident from the fact that 4-methoxy-2-chloropyrimidine (**299**) is the "sole" product^{477b} formed on treatment of 2,4-dichloropyrimidine in methanol with one mole of sodium methoxide^{181, 517a} at 25°; cf. a whole series of reactions with alkoxides (30°, 80 min, 85–95% yields)^{517b} and phenylmercaptides (–5°, 2 hr, 70–80% yields).^{517c} Dimethoxylation of both the 2,4- and 4,6-dichloro compounds⁵¹⁸ proceeds at 25° with two moles of methoxide ion. It is interesting to note that reaction of non-basified methanol with 2,4-dichloropyrimidine gives about equal amounts of 2- and 4-methoxylation.¹⁸¹ Under these conditions of acid-catalyzed reaction, the electrostatic effect (Section II, B, 4 and II, C) or hydrogen bonding of the nucleophile (solvent in this case) to the more basic 1-nitrogen (**300**) facilitates reaction at the 2-position and an approximate equalization of rates occurs. With methanolic methoxide, hydrogen bonding of the solvent to this ring-nitrogen will sterically hinder reaction at the less activated 2-position.



[299]



[300]



[301]

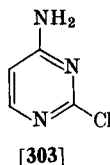
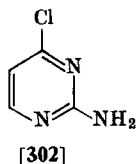
Our results on the reaction of 2,4-dichloropyrimidine with another anion should be pointed out in connection with the fallacy of considering "sole product (isolated)" to mean absolute selectivity.^{477b} From the reaction of 2,4-dichloropyrimidine with sulfanilamide anion in molten acetamide (65°, 1 hr), the major product, 2-chloro-4-sulfanilamidopyrimidine, is isolated in good yield; paper chromato-

graphy demonstrated a 10:1 ratio of reaction at the 4- and 2-positions, respectively.⁵¹⁹

Mono-alkoxylation of 2,4,6-trichloropyrimidine with methoxide⁵²⁰ or ethoxide ion⁵²¹ occurs "only"^{477b} at the 4-position and one (0°), two (25°), and three moles (70–100°) of methanolic sodium methoxide yield 2,4-dichloro-6-methoxy- (**301**),⁵²⁰ 4-chloro-2,6-dimethoxy-,^{522, 523} and 2,4,6-trimethoxy-pyrimidine,⁵²⁴ respectively. Progressively more vigorous conditions are required as the ring is deactivated by introduction of electron-donating (nucleophilic) substituents. The selective effect of deactivation leads to 2-amination and 2-alkoxylation of 4-alkoxy-, 4-amino- or 4-substituted-amino-2,6-dichloropyrimidines. Amination at the 4-methoxy group of 2,5-dichloro-4-methoxypyrimidine with methanolic ammonia (80°, 3 hr, high yield)^{288b} is noteworthy. As noted and explained in Section II, E, 2, c, a 5-nitro group in these 4-substitution products leads to selective 6-*amination* due to hydrogen bonding^{97c} or electrostatic attraction in the transition state. In 2,4,6-trifluoropyrimidine and in its 2,4,5-trichloro and 2,4,5,6-tetrachloro and -tetrafluoro analogs, the initial 4-substitution by alkoxide ion is followed by 2-substitution at slightly higher temperatures.²⁷⁷ With sulfanilamide and *N*⁴-acylsulfanilamide anions, 2,4,5- and 2,4,6-trichloropyrimidine monosubstitute to at least 70% in the 4-position but 3–20% of 2-substitution was also noted.^{288b, 388a–388c}

The kinetic comparison¹⁶⁷ of substitution of 2- and 4-chloropyrimidines with piperidine and morpholine in alcohol revealed a 10-fold greater reactivity of the latter plus the intervention, under certain conditions, of the previously observed²⁴⁴ acid catalysis. From this reactivity relation, it seems clear that the *additional* hydrogen bonding and electrostatic attraction possible in the 2-pyrimidinyl transition state for aminations is not great enough to overcome the greater activation at the 4-position and the steric effect on the 2-position of hydrogen bonding of the solvent to the ring-nitrogen. A comparison of alkoxylation with this amination in aprotic solvents is needed to determine the effect of hydrogen bonding and electrostatic attraction in the latter substitution.

These factors are sufficient to produce similar amounts of aminated isomers from 2,4-dichloropyrimidine which gives predominantly 4-alkoxylation products. Thus, a mixture of 2-amino-4-chloro- (**302**) and 4-amino-2-chloro-pyrimidine (**303**) is obtained on treatment of 2,4-dichloropyrimidine with alcoholic ammonia (25°, < 18 hr),⁵²⁵ the reagent here being better at hydrogen bonding than piperidine.



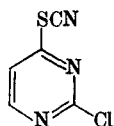
Yields of 60% and 40%, respectively, were calculated on the basis of product stabilities, but actually 11% and 29% of the 2- and 4-amino derivatives, respectively, were isolated. Similarly (95°, 5 hr), the 6-methyl homolog gives 28% of 2-amino-4-chloro- and 32% of 4-amino-2-chloro-6-methylpyrimidine,⁵²⁶ but other work (summarized in ref. 527) in various solvents reported only 4-substitution.⁴⁹⁸ Koppel *et al.*⁵²⁷ found that, in spite of presumed steric hindrance (actually it is slight), dimethylamine (25% aqueous, 25°, 1 hr) displaced the 4-substituent from 2,4-dichloro-5-methylpyrimidine. The product was isolated in about 90% yield and was homogeneous in three paper chromatographic systems. This result we attribute to steric hindrance to reaction at the 2-position resulting from hydrogen bonding of the solvent to the pyrimidine-nitrogens. It is possible that the methyl group may also contribute to the result by having an unequal deactivating effect.

The influence of (a) hydrogen bonding of the solvent to an azine-nitrogen in *decreasing* reaction at the adjacent carbon and (b) of hydrogen bonding of an amine reagent, especially in aprotic solvents, in *increasing* reaction at the adjacent carbon warrants further investigation. The significance of hydrogen bonding of water to an azine-nitrogen (cf. Section II, C) is suggested by the results of various aminations in this section including those discussed below. Amination of 2,4,6-trichloropyrimidine (alcoholic NH₃, 20–100°, “several” hr) gives a 2:1 mixture of 2-amino-4,6-dichloro- and 4-amino-2,6-dichloro-pyrimidine.⁵²⁸ Methylamine and dimethylamine (aqueous solution, 20°) gave 1:2 (or unspecified) mixtures of 2- and 4-substitution products^{329, 521, 529} in 80% (or unspecified) yields. On the other hand, aniline in alcohol (20°, 2 hr) gave 4-substitution (50% yield).⁵²¹ 2,4,5,6-Tetrachloropyrimidine gave only 4-substitution with aqueous aniline (35°, “short time,” 86% yield), aqueous ammonia (80°, 2 hr), aqueous diethylamine (35°, ca. 1 hr), and aqueous *n*-butylamine (35°, ca. 1 hr) but in unspecified yield with the last three reagents.³⁷⁷ Only 4-substitution was reported^{276a, 277, 378, 530} for the reaction of 2,4,6-trifluoro-, 2,4,5-trichloro-, and 2,4,5,6-tetrafluoro-

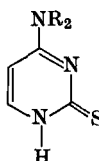
pyrimidines with ethereal ammonia (20°, 30 min, 36% yield) or dimethylamine (0°, 1 hr, 62% yield) and alcoholic hydrazine hydrate (25°, 62% yield). It should be pointed out that the mono-substitution products from 2,4,6-trichloro-, 2,4,5,6-tetrachloro-, and 5-chloro-2,4,6-trifluoro-pyrimidines with tertiary amines in hydrocarbons were *assumed* by Kober and Raetz⁴⁹³ to be 2-derivatives.

A careful re-examination of the reaction of 2,4,6-trichloropyrimidine with ethyleneimine (*benzene*, 30°, 30 min) by Koppel *et al.*³²⁵ has shown that mono-substitution occurs only at the 4-position (**184**) (70% yield and no 2-substitution by paper chromatography). An earlier report⁵³¹ that 2-substitution in *water* predominated by 5:1 is believed by these workers to be erroneous, the lower melting "2-isomer" actually being impure 4-ethyleneimino derivative.

2-Chloropyrimidine is aminated with alcoholic ammonia at 130° while 4-chloro-2-methyl- and 4-chloro-6-methyl-pyrimidine yield the corresponding 4-amino derivatives at 100°. ²¹⁸ 4-Aminopyrimidine is not prepared from the chloro analog because of facile self-quaternization (see Section III, B, 2 for comments on factors involved) of the latter.



[304]



[305]

Other types of leaving groups and of nucleophilic reagents also show greater reactivity at the 4-position: 2,4-dichloropyrimidine with alcoholic potassium thiocyanate⁴⁰⁰ (to **304**) and with chemical monodehalogenation (zinc and ammonia or ammonium chloride),^{454, 526, 532} 2,4-(1*H*,3*H*)-pyrimidinedithione with ammonia or amines^{326–328, 533} to give **305**, 2,4-(1*H*,3*H*)-pyrimidinedione thionation^{309, 310} with phosphorus pentasulfide (cf. **126** and **127**), pyrimidine with phenyl lithium,⁴⁷⁴ and 2,4,6-trichloropyrimidine with several sulfanilamide anions.^{388a–388c} In the latter reaction, the absence of a hydrogen-bonding solvent (cf. Section II, B, 3) equalizes 2- and 4-substitution; in the presence of water generated from K₂CO₃ and the acidic sulfonamide, the 4-sulfonamido compound predominates^{388c} by 5 to 1.

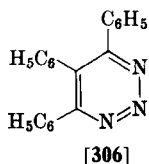
Various nucleophilic reactions of polysubstituted 5-halopyrimidines are described in Section II, E, 2, e with postulates to explain the degree of reactivity. For pyrimidine derivatives, the effect of the following on nucleophilic substitution is included in earlier sections: hydrogen bonding and cationization in Section II, C, the leaving group in Section II, D, and the nucleophile in Sections II, E, 2, e and II, F.

c. *Pyrazine*. The single kind of ring-position in pyrazine (**270**) is more reactive than the 2-position of pyridine (**272**) and less reactive than 2- or 4-position of pyrimidine (cf. Section III, A, 2). It should be and appears to be about as reactive as the 3-position of pyridazine but less reactive than the 4-position (**268**).

Methoxylation of 2,5- and 2,3-dibromopyrazines^{223b, 373} provides the basis for a comparison of *ortho* and *para* direct deactivation (Section II, E, 2, e) in the mono-methoxy derivatives such as **198** and **199**. Pyrazine derivatives are discussed in Sections II, C and II, D.

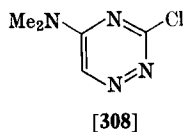
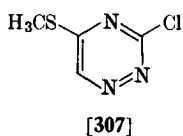
4. Triazines

a. *v-Triazine*. The only aromatic *v*-triazine known is the triphenyl derivative⁵³⁴ **306**. The reactivity relation to other azines is postulated in Scheme I, p. 266.



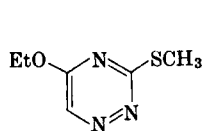
b. *as-Triazine*. 5- and 3-*as*-Triazinyl derivatives (**261** and **263**) are more reactive than pyrimidines and other diazines, and the 6-*as*-triazinyl compounds (**267**) are estimated to be as reactive as 2- and 4-substituted pyrimidines but more reactive than other diazines. Consideration of charge stabilization in the transition state leads to the postulation that the order of reactivity of the three different ring-positions should be 5- > 3- > 6-position. This relationship is consistent with the reactivity of 3,5-disubstituted and 3,5,6-trichloro derivatives in those cases where the structures of the products have been established. However, some nucleophilic substitutions⁴⁹² of the former have been *assumed* to give reaction at the 3-position. The analogy cited was the behavior of the corresponding pyrimidine derivatives, which,

however, clearly suggests the reverse (cf. Section III, B, 3, b). The relation of the reactivity of *as*-triazine to *s*-triazine derivatives is not clear. Two papers^{492, 535} state that halo-*as*-triazines are the more reactive, but no supporting comparative data were given. One statement⁴⁹² appears to be based on the tendency of 3,5-dichloro-*as*-triazine toward self-quaternization in which the greater basicity (cf. factors discussed in Section III, B, 2) could conceivably produce greater instability. 3,5-Dichloro-*as*-triazine is readily hydrolyzed by water as is 2,4-dichloro-*s*-triazine.^{536, 537} 3-Chloro-5,6-diphenyl-*as*-triazine was stated⁵³⁵ to be more reactive toward non-basified methanol or ethanol (complete reaction required 4.5 hr at reflux temperature) than the corresponding *s*-triazine (no data given). This reaction involves the relative susceptibilities to acid catalysis in addition to the relative reactivities. If *as*-triazines are more reactive than *s*-triazines in these instances due to the superposition of the factors mentioned, a general conclusion to this effect is not justified on the basis of the qualitative information available or theoretical considerations. The latter predict greater activation by resonance stabilization (*s*-triazine, **258**) than by inductive stabilization (*as*-triazine, or **261** or **263**) of the negative charge in the transition state, a conclusion supported by the kinetic data (Section III, A, 2) on 2- or 4-substituted pyridines vs. 3-substituted pyridines and on 2- or 4-substituted pyrimidines vs. 2-substituted pyrazines. 3-*s*-Tetrazinyl compounds (**260**) are expected to be more reactive than 3-*as*-triazinyl compounds (**263**), with the 5-*as*-triazinyl derivatives (**261**) being intermediate in reactivity.

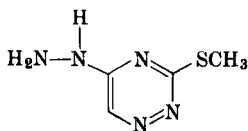


Sodium methyl mercaptide in xylene was reported⁴⁹² to react (25°, 2 hr) in a stepwise fashion with 3,5-dichloro-*as*-triazine to yield the 3-methylthio-5-chloro and then (70°, 2 hr) the 3,5-bis-methylthio derivatives. However, the structure of the former is very likely to be **307**. With dimethylamine in benzene (25°, 5 min), ethyleneimine in ether (25°, 3 min), and alcoholic ammonia (25°, few min), this dichloro derivative was *assumed* to form 3-amino derivatives.⁴⁹² The high reactivity of *as*-triazines is demonstrated by the facile ethoxylation

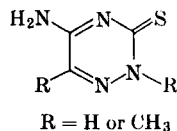
(25°, 30 min) of the deactivated 3(5)-dimethylamino-5(3)-chloro compound⁴⁹² which probably has structure **308**. 3,5-Dichloro-*as*-triazine reacts in the cold with ethanolic methylmercaptide under neutral conditions to give the bis-methylthio derivative, but under alkaline conditions (25–40°, > 2 hr) an ethoxy-thiomethyl derivative is formed. If stepwise substitution occurred, the assumed structure 3-ethoxy-5-methylthio-*as*-triazine would undoubtedly be correct since the first reaction would occur at the 5-position with the more reactive nucleophile, methylmercaptide ion. However, the results of the two experiments suggest that ethoxy substitution of the bis-methylthio derivative took place and that the more reactive 5-methylthio group was displaced to give **309**. The mono-hydrazino derivative prepared (aqueous alcoholic N₂H₄, 78°, 4 hr, 25% yield) from 3,5-bis-methylthio-*as*-triazine was assumed⁵³⁸ to be the 5-substitution product (**310**) on the basis of the proved structure of the



[309]



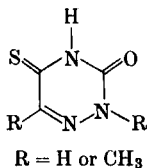
[310]



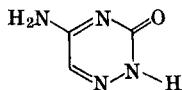
[311]

5-amino derivatives (**311**) obtained by alcoholic amination (100°, 16 hr, 85–100% yields) of 6-methyl-*as*-triazine-3,5-dithione⁵³⁹ and its 2-methyl isomer.⁵⁴⁰

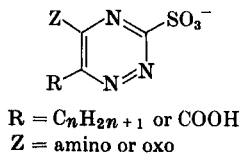
Another nucleophilic substitution demonstrating greater reactivity at the 5-position is nucleophilic thionation (via cationized forms of polythiophosphoryloxy intermediates such as structure **126**) of *as*-triazine-3,5-dione^{310, 311} and of its 2-methyl⁵⁴⁰ and 6-methyl derivatives⁵³⁹ to form **312** in 50–100% yields. Thionation at the 3-position



[312]



[313]



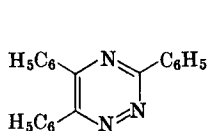
[314]

can be accomplished if a higher temperature and a longer reaction time are used. The effect of structure on this reaction of *as*-triazines has been recently reviewed.⁵⁴¹ A methylthio group in the 5- or 3-position is more reactive toward aqueous acid⁵⁴² or toward alkali,⁵³⁹ amines,⁵⁴³ or hydrazine⁵³⁸ than are the thione analogs.

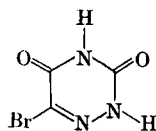
The high level of reactivity of *as*-triazines is also indicated by 5-substitution of **312** with ammonia or amines (110°, 20 hr, 40–65% yield)^{310, 539, 544} and with hydroxylamine or hydrazine (65–80°, 2–4 hr, up to 84% yield)⁵⁴⁴ and by the facile acid hydrolysis⁵⁴⁵ of the *S*-methyl derivative of **312**. The much easier hydrolysis (acid or alkali) of **313** compared to the pyrimidine analog has been noted.^{539, 540}

3-Chloro-5,6-diphenyl-*as*-triazine readily undergoes methoxy-dechlorination at 25° (< 12 hr) with methanolic methoxide⁵⁴⁶ and at 65° (4.5 hr) in non-basified methanol.⁵³⁵ The chloro group is also displaced⁵³⁵ by hydrazine (80°, 1 hr), ammonia (140°, 6 hr), and phenylmagnesium bromide (70°, 12 hr), the latter forming the triphenyl compound **315**. 3-Chloro-6-phenyl-*as*-triazine is unstable to cold water or alkali and to hot alcohol or aqueous potassium carbonate.⁵⁴⁷ 3-Methylthio and 3-carboxymethylthio substituents are easily hydrolyzed, the latter much more readily (cf. **136** and **237**) but only in acid.^{542, 548} A 3-sulfonic acid group (cf. **314**) is readily displaced, especially in acid solution.^{539, 542, 545, 549} Conversion of 3-amino-5,6-diphenyl-*as*-triazine into the 3-oxo analog with alkali proceeds²⁸¹ rather easily (100°, < 4 hr), as it does with other amino-azines.

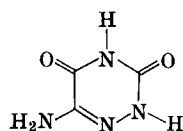
Substituents in the 6-position (cf. **267**) show appreciable reactivity. 6-Bromo-*as*-triazine-3,5(2*H*,4*H*)-dione (**316**) undergoes 6-substitution with secondary amines or hydrazine,^{430a, 550} with mercaptide anions or thiourea (78°, 16 hr),^{430a, 551} with molten ammonium acetate⁵⁵² (170°, 24 hr, 53% yield), and with chloride ion^{552, 553} during phosphorous oxychloride treatment to form 3,5,6-trichloro-*as*-triazine. The latter was characterized as the chloro analog of **316** by treatment with methanol (20°, heat evolution) and hydrolysis (neutral or acid) to the dioxo compound.^{552, 553} The mercapto substituent in 6-mercapto-*as*-triazine-3,5(2*H*,4*H*)-dione is displaced by secondary



[315]



[316]

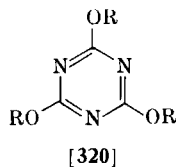
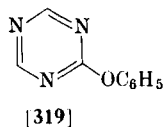
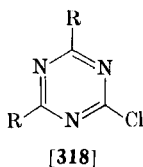


[317]

amines or hydrazine,⁵⁵⁰ and the 6-amino analog (317) is easily hydrolyzed (1*N* alkali, 100°, 2 hr) to the corresponding trioxo compound.⁵⁵²

Nucleophilic substitution of *as*-triazines is discussed in relation to hydrogen bonding and the effects of the leaving group and of other nuclear substituents in Sections II, C, D, and E, respectively.

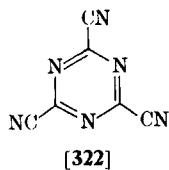
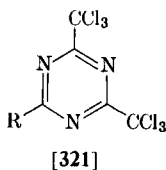
c. *s*-Triazine. The high reactivity of *s*-triazine derivatives (2-, 4-, and 6-positions identical) is understandable since maximal resonance stabilization of a charge can be achieved in the transition state. *s*-Triazines are more reactive than diazines on the qualitative basis of preparative organic chemistry and from the meager kinetic data available. The relationship of the reactivity of 2-substituted-*s*-triazines to that of 3-substituted *s*-tetrazines will depend on the quantitative effect (cf. Section III, A, 2) of one *para* resonance-stabilizing ring-nitrogen vs. two *meta* induction-stabilizing ring-nitrogens. Reactivity is expected to be greater for *s*-triazines than for all three *as*-triazine positions, with the difference being smallest for 5-substituted *as*-triazines. Even the deactivated mono- and di-substitution products of trichloro-*s*-triazine show high reactivity, trisubstitution sometimes proceeding to completion rapidly at 20°. Triazines bearing one or more halo, trihalomethyl, cyano, alkoxy, or alkylthio substituent are very reactive even below 20°.



Because of the ease of ring synthesis, symmetrically trisubstituted *s*-triazines have been more thoroughly studied, but a few nucleophilic substitutions of derivatives bearing a single leaving group are known. 2-Chloro-4,6-diphenyl- and 2-chloro-4,6-dimethyl-*s*-triazines (318) undergo facile nucleophilic displacements with ammonia, amines, and hydrazine,^{271, 443d, 554} with alkoxide,²⁷¹ or with hydrosulfide ions.⁵⁵⁵ A convenient synthesis of monoamino-*s*-triazines in high yield is the reaction of 2-phenoxy-*s*-triazine (319) with ammonia or aliphatic amines (30–70°) or with aniline (120°).⁵⁵⁶ Triphenoxy-*s*-triazine (320) reacts with all classes of amines⁵⁵⁷ without side-reactions

while the alkoxy analogs undergo extensive dealkylation^{303b} especially with weakly basic amines; the former can be aminated at 150–200° in very high yield. 2-Chloro-4,6-bis-haloalkyl-*s*-triazines react at the 2-position at rates increasing with the degree of halogen substitution of the alkyls and with the electronegativity of the halogen (per-fluoroalkyl > perchloroalkyl).²⁷¹ The nucleophiles investigated were non-basified ethanol (65°, 0.5 hr), ethoxide ion (20°, very fast), amines (20°, 3 hr), hydroxylamine or hydrazine (0°, very fast), and thiocyanate (50°, 20 min). With more ethoxide ion, with hydroxide ion, or with amines (20–150°, depending on the amine) in aprotic solvents, all of the perhaloalkyl substituents can also be displaced.^{270, 271, 424}

2,4-Dichloro-*s*-triazine^{536, 537} and its 6-alkyl analogs⁵⁵⁸ are as easily hydrolyzed by water as trichloro-*s*-triazine and, on suspension in aqueous ammonia (25°, 16 hr), the first is diaminated in good yield. 2,4-Bistrichloromethyl-6-methyl- and -6-phenyl-*s*-triazines (**321**) require a special procedure⁴²⁴ for mono-alkoxylation (0–20°, 16 hr, alcoholic triethylamine); disubstitution occurs at reflux temperature (8 hr). Aqueous triethylamine (100°, 3 hr) causes complete hydroxylation of 2,4,6-tris-trichloromethyl-*s*-triazine⁴²⁴ which can be mono-substituted⁵⁵⁹ with ammonia, methylamine, or phenoxide ion at 20°.

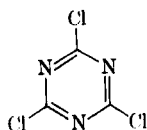


2,4,6-Tricyano-*s*-triazine (**322**) is mono-substituted very rapidly with anhydrous methanol (20°, few min) and with water; di- and tri-substitution products also result under mild conditions⁵⁶⁰ (65°, one min, and 65°, several hr, respectively, for methanol).

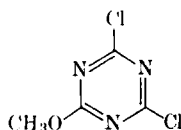
The reactivity of cyanuric chloride (2,4,6-trichloro-*s*-triazine) as an indication of *s*-triazine activation is misleadingly high because of mutual activation of the chlorines (*meta* activation > *ortho* or *para* activation) and its symmetry (cf. Section III, A, 1). However, the greatest variety of nucleophilic substitutions have been investigated with this substrate.

2,4,6-Trichloro-*s*-triazine (**323**) in cold 57% hydriodic acid yields

2,4,6-triiodo and 2,4-diiodo-6-chloro derivatives.⁵⁶¹ Other acid-catalyzed reactions of *s*-triazines are discussed in Sections II, C and III, A, 2. The reaction of carboxylic acids (or their anions) with this substrate leads to cyanuric acid (*s*-triazine-2,4,6(1*H*,3*H*,5*H*)-trione) and acid chlorides.^{562,563}



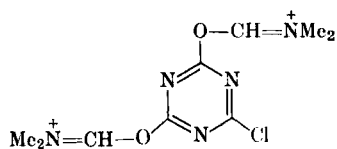
[323]



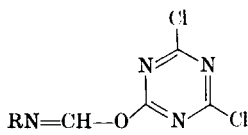
[324]

Mono-substitution occurs most readily in the stepwise replacement of the halogen substituents of 2,4,6-trichloro-*s*-triazine: with aqueous methanol and sodium bicarbonate (30°, 30 min), the monomethoxy derivative (324) is obtained; on heating (65°, 30 min), the disubstituted derivative is formed; and on brief heating (65°) with the more basic sodium carbonate or methanolic sodium hydroxide (25°, 3 hr) complete methoxylation (320) occurs.⁵⁶⁴ Ethanolic ethoxide (25°, 1 hr) or sodium carbonate (35°) is sufficient to give complete ethoxy-dechlorination.⁵⁶⁴ The corresponding phenoxy derivatives are obtained on treatment with one (0°), two (15°, 1 hr), or three equivalents (25–70°, 3 hr) of various sodium phenoxides in aqueous acetone.⁵⁶⁵ The stepwise reaction with phenols, alcohols, or thiols proceeds in better yield in organic solvents (acetone or chloroform) with collidine or 2,6-lutidine as acid acceptors than in aqueous sodium bicarbonate.^{566,567}

Other oxygen nucleophiles demonstrating high reactivity toward 2,4,6-trichloro-*s*-triazine are: *N,N*-dimethylformamide (10° > 0.5 hr) giving rapid disubstitution (325); *N*-alkylformamide (20°, 4 hr) in



[325]

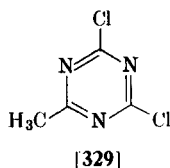
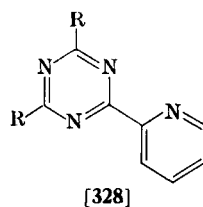
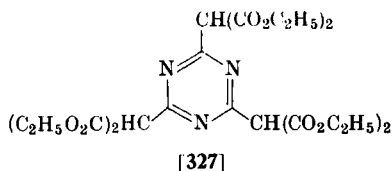


[326]

acetone-alkali giving similar mono-substitution (326) and subsequent decomposition to 4,6-dichloro-*s*-triazin-2(1*H*)-one and isonitriles⁵⁶⁸; and mono-substitution with alkyl phosphate dianions in cold alcoholic alkali.⁵⁶⁹

The trichloro derivative reacts rapidly at room temperature with sulfide, hydrosulfide, alkylmercaptide, or thiophenoxide ions in the solid phase, in water, or in organic solvents.^{570, 571}

2,4,6-Trichloro-*s*-triazine also reacts readily with carbon or phosphorus nucleophiles. Diethylmalonate anion forms a mono-derivative under mild conditions and the tri-substitution product (**327**) under vigorous conditions with excess nucleophile.⁵⁵⁸ Nucleophilic attack by the π -electrons of ketene diethylacetal^{477a} to give **254** and of dimethylaniline^{361c, 476} to give **253** has been mentioned earlier. Two



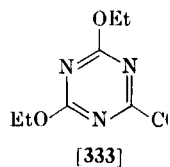
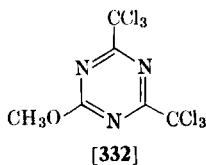
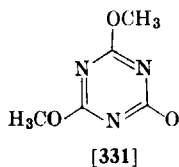
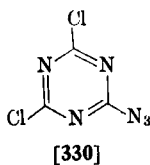
papers^{572, 573} indicate an unlikely nucleophilic attack by the 2- or 4-position of pyridine to yield products, *assumed* to be 2-(2'- or 4'-pyridyl)-4,6-disubstituted-*s*-triazines (**328**). However, the formation of these *red* products requires the presence of water, strongly suggesting that the pyridine ring opens to give glutacondialdehyde derivatives (which are generally red) rather than compounds with the structures assigned. Diazomethane and diazoethane react readily at 0–20° to form 2-diazoalkyl-4,6-dichloro-*s*-triazines (**255**).³⁶⁸ Other reactive carbon nucleophiles are alkyl- and aryl-magnesium halides. Grignard reagents have been employed with cyanuric chloride and with mono- and di-chloro analogs to introduce two^{556, 574} or three (in benzene solution, 70°, 12 hr) aryl groups.^{535, 575} As is true for nucleophilic substitution in general, the first step proceeds most easily. Methyl- and ethyl-magnesium bromides mono-substitute trichloro-*s*-triazine readily⁵⁵⁶ yielding **329**. Triethylation of 2,4,6-tribromo-*s*-triazine on heating with ethylmagnesium iodide has been reported.^{576a} 2-Chloro-4,6-bis-trichloromethyl-*s*-triazine reacts at the 2-position

with trialkyl phosphites,²⁷¹ and trichloro-*s*-triazine can be mono- or tri-substituted to give the Arbuzov phosphonate derivatives.^{576b}

2,4,6-Trichloro-*s*-triazine is mono-aminated at temperatures of -15° to 100° , depending on the nucleophilicity of the amine and on the solvent.^{270, 395, 396} With ammonia and alkylamines, one chloro group is replaced at -15 to 10° , a second at 10 – 50° , and a third at 20 – 100° .^{303c, 303d, 577} Unsymmetrical triamino derivatives can be prepared^{578a} by adding one mole of three different amines to the reaction mixture at each of the three temperatures. The tribromo analog is stated⁵⁷⁷ to react more rapidly than cyanuric chloride with ammonia or primary and secondary amines. Toward ammonia, methoxide ion, or water, the trifluoro analog is also qualitatively more reactive^{578b}; with ammonia (0° , 1 hr) mono-amination occurred in ether and di-amination in tetrahydrofuran.⁵⁷⁹

Azide ion is a rather weak nitrogen nucleophile, but in aqueous acetone (20° , 5 min) it readily produces 2-azido-4,6-dichloro-*s*-triazine^{302a} (**330**) and also yields more slowly (0° , 12 hr, 90% yield) the 2,4,6-triazido-*s*-triazine.^{301, 580} The latter is rapidly hydrolyzed³⁰⁰ (50°) to cyanuric acid and is easily mono-aminated^{302a} (0° , 1 hr, in ether).

Even polyalkoxy-*s*-triazines are quite prone to nucleophilic substitution. For example, 2,4,6-trimethoxy-*s*-triazine (**320**) is rapidly hydrolyzed (20° , dilute aqueous alkali) to the anion of 4,6-dimethoxy-*s*-triazin-2(1*H*)-one (**331**). This reaction is undoubtedly an S_NAr2 reaction and not an aliphatic S_N2 dealkylation. The latter type occurs with anilines at much higher temperatures (150 – 200°) and with chloride ion in the reaction of non-basified alcohols with cyanuric chloride at reflux temperatures. The reported⁵⁸¹ dealkylation with methoxide has been shown⁵¹⁹ to be hydrolysis by traces of water present. Several analogous "dealkylations" by alkoxide ion, reported without evidence for the formation of the dialkyl ether, are all associated with the *high reactivity* of the alkoxy compounds which are, in fact, hydrolyzed by usually tolerable traces of water. Brown⁵⁸²



has discussed this type of reaction with pyrimidines, the most pertinent example being 2,4-diethoxy-5-nitropyrimidine.

Nucleophilic trans-etherification of alkoxy-*s*-triazines occurs in a few minutes at the boiling point of various alcohols, either molar or catalytic amounts of alkoxide^{564,583} or triethylamine⁴²⁴ being used. This reaction occurs during attempts⁴²⁴ to prepare unsymmetrical polyalkoxy compounds; e.g., **333** is formed from **332**.

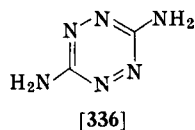
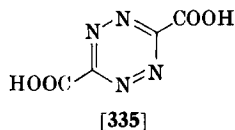
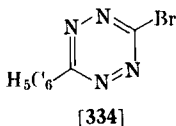
2,4,6-Tris-methylthio-*s*-triazine undergoes similar displacement with methanolic methoxide.⁵⁸³ Its methylthio groups are substituted with sodium sulfide⁵⁸⁴ and with ammonia.^{584, 585} Methylthio and carboxymethylthio substituents are readily hydrolyzed by dilute acid.^{584,586}

The effects of the following on nucleophilic substitution of *s*-triazines are discussed elsewhere: hydrogen bonding and cationization (Sections II, C and III, A, 2), the leaving group (Section II, D), other nuclear substituents (Section II, E), and the nucleophile (Section II, F).

5. Tetrazines

a. *v*- and *as*-Tetrazines. Aromatic 1,2,3,4- and 1,2,3,5-tetrazines are unknown.

b. *s*-Tetrazine. The few known nucleophilic substitutions of 1,2,4,5- or *s*-tetrazines (**260**) are facile. Reactivity approximately equivalent to *s*-triazines is to be expected since the charge is stabilized in the transition state by two "resonance" and two "inductive" nitrogen atoms. The identical 3- and 6-positions are activated by one more ring-nitrogen than those in *as*-triazines. Appreciable hydrogen bonding to the azine lone-pairs has been demonstrated for tetrazines (Section II, C), but its effect on the reactivity toward nucleophiles is unknown.



3-Bromo-6-phenyl-*s*-tetrazine⁵⁸⁷ (**334**) gives the 3-hydroxy analog in quantitative yield after a few minutes at 95° in ethanolic potassium hydroxide or ethanolic ethoxide. As with other highly activated alkoxy-azines (cf. Section III, B, 4, c and reference 582), the latter

result is undoubtedly produced by alkoxylation followed by hydrolysis by traces of water present. Amino derivatives are formed immediately in quantitative yield on treatment of the bromo compound at room temperature with liquid diethylamine, ammonia in benzene, or ethyleneimine in benzene containing triethylamine. Various other aminations of this bromotetrazine and of substituted phenyl analogs proceed under similar conditions. The high reactivity is attributable to the tetrazine ring, the effect of the phenyl group being negligible (Section II, E).

The electron-deficient nature of the *s*-tetrazine ring-carbons is indicated by formation of a dipotassium salt⁵⁸⁸ ($C_2N_4K_2$) of tetrazine in liquid ammonia, by easy decarboxylation of the 3,6-dicarboxylic acid⁵⁸⁹ (335), and by the very weak basicity of the 3,6-diamine⁵⁹⁰ (336).

Tetrazine itself is red due to an $n \rightarrow \pi^*$ electronic transition with an absorption maximum at $542\text{ m}\mu$ ($\log \epsilon_{\text{max}}, 2.9$).^{173d, 591} The wavelength of this transition is related to the electron-attracting nature of the ring and it increases with the number of azine-nitrogens: pyridine, $290\text{ m}\mu$; pyrimidine, $310\text{ m}\mu$; pyridazine, $338\text{ m}\mu$; *as*-triazine, $383\text{ m}\mu$ (calcd.); *v*-triazine, $433\text{ m}\mu$ (calcd.); and pentazine, $865\text{ m}\mu$ (calcd.).⁵⁹¹

6. Pentazine

No aromatic pentazines are known. From the relative reactivities of the other monocyclic azines, it is expected that pentazine (256) should be the most reactive toward nucleophilic substitution since it has the maximal number of ring-nitrogens. However, for the same reason, the pentazine ring should also be very susceptible to nucleophilic ring-opening, and it should be a stronger dehydrogenating agent than tetrazine and more thermally unstable.

IV. Reactivity in Bicyclic Azines

A. KINETIC DATA AND RELATION OF RINGS AND RING-POSITIONS. AN ACTIVATION-NUMBERING SYSTEM

In bicyclic azines, as in the monocyclic azines already discussed, the faster of two nucleophilic substitutions proceeds via the transition state which has the lower free energy (with respect to the reactants) due to the stabilizing effects of resonance, hydrogen bonding, or electrostatic attractions. Different nucleophiles and different leaving

groups follow the same pattern of relative positional reactivity unless acid catalysis, a cyclic transition state, or a different charge-type comes into play.

Relative reactivity can be altered by a change in the rate-determining step since the relative rates of removal of the leaving group are not necessarily the same as the relative rates of attack of the nucleophile. Radio-isotope exchange should be extremely useful for determining the kinetic parameters of the first stage of S_NAr2 reactions since the bonds to the nucleophile and to the leaving group broken in the second stage are almost identical. In the absence of relevant data, the possibility needs to be considered that some reactions of nucleophiles with azines and azinium compounds might be thermodynamically controlled equilibria.

The alteration of nucleophilic reactivity by the intervention of "covalent hydration" and analogous nucleophilic additions^{11b, 150} needs to be borne in mind for many polyazaphthalenes. Covalent hydration has been observed in several bicyclic azines besides pteridine and quinazoline (Section IV, B) and is related to nucleophilic substitution in activation and in proceeding through the same first stage as S_NAr2 reactions. The Bucherer interconversion of naphthols and naphthylamines involves exchange of oxygen and nitrogen substituents in a covalent adduct produced by bisulfite ion.^{592b}

The energy of activation decreases and the rate of nucleophilic substitution increases with insertion of a nitrogen atom anywhere in the naphthalene skeleton, and both changes are greater the more nitrogen atoms present. There is possibly a small decrease in the activating effect of *additional* ring-nitrogens. Marked variations in the entropy of activation have been found to control the reaction rate of certain ethoxylations (Section IV, A, 2).

Conclusions and predictions of the reactivity in bicyclic azines are based on (a) kinetic data (Section IV, A, 2) (b) qualitative or semi-quantitative indications from preparative organic chemistry (Section IV, B), and (c) considerations of the reaction mechanism (Sections II, B and III, A). The relative reactivity in poly-substituted compounds gives a misleading indication of the relative reactivity in the mono-substituted analogs since the substituents have sizeable and *unequal* effects on each other even when all the substituents are the same. The effect of substituents cannot be disregarded since even weakly activating and deactivating substituents have effects of the same order of magnitude as inductive activation and internuclear⁵⁹⁷ resonance

activation by a ring-nitrogen in bicyclic compounds. However, the effect of substituents in the adjoining ring will be diminished in transmission. The reactivity of bicyclic compounds is made easier to understand and interpret by means of an activation-numbering system presented at the end of this subsection.

The relation of the activation by a nitro group to that by an azine-nitrogen in various bicyclic positions provides information in support of that available from studies of azines and forms the basis for certain predictions of azine reactivity. The data tabulated in Section IV, A, 2 also provide a few comparisons of leaving groups, nucleophiles, and deactivating and activating substituents (cf. Sections II, E and III, A, 2).

Where "ortho effects" and special entropy factors control the relation of the reaction rates, it seems more appropriate to evaluate relative activation from the energies of activation.

1. Summary of Relative Reactivity at Different Ring-Positions. A Proposed Activation-Numbering System. Reactivity Factors

Nucleophilic substitution of bicyclic azines can be summarized by the following generalizations:

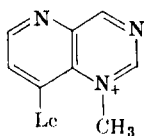
- (1) When the azine-nitrogen and leaving group are in the same ring,
 - (a) resonance activation (*ortho* or *para* to a ring-nitrogen) is greater than inductive activation (*meta* to a ring-nitrogen) by 10^3 – 10^5 -fold in reaction rate,
 - (b) resonance activation by a ring-nitrogen is greater (in terms of E_A) when it is *para* to the leaving group than when it is *ortho* to it, the magnitude of the difference varying with the number and orientation of the ring-nitrogens,
 - (c) reactivity is greater *ortho* to an azine-nitrogen with organometallic reagents^{592b, 593–596} (cf. Section IV, B) which can form cyclic transition states,
 - (d) the "benzo group" in benzoazines produces a substantial activation (10–1,000 times greater rates) relative to the monocyclic azine (generalization 2 below is the exception),
 - (e) inductive activation (10^2 – 10^4 -fold increase in rate) in the same ring is not appreciably affected by benzo-fusion.
- (2) When an azine-nitrogen and a leaving group are in the 2,3-relation to each other in monoaza- and polyaza-naphthalenes, there is a dramatic effect on the reaction rate (for 3-chloroisoquinoline 10^3 – 10^5 -fold less than for its 1-chloro isomer and for 2-chloroquinoline 200–400-fold less than for 2-chloropyridine) due to restrictions imposed on the resonance stabilization of charge in the transition state by the bicyclic system;

in the two comparisons reported, the activation (by a 2-NO₂ group of a 3-Br substituent in naphthalene) gives about 15 times the rate produced by internuclear⁵⁹⁷ resonance activation (2-NO₂-6-Br- and 1-NO₂-7-Br-naphthalene); this 2,3-resonance activation is still greater than both intra- and inter-nuclear⁵⁹⁷ inductive activation but only by two orders of magnitude in the one comparison available.

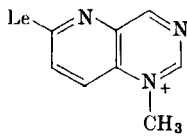
- (3) When activation is transmitted from the adjoining ring,
 - (a) all positions are activated to a detectable extent,
 - (b) the inductive effect seems to be related to the intervening distance in space and, in comparison to the intranuclear effect, is reduced only in proportion to the small increase in distance; thus 4-chloroisoquinoline and 3- and 8-chloroquinoline are equal in inductive activation and the three isomers (5- and 7-chloroisoquinoline and 6-chloroquinoline) are inductively activated only about half as much in terms of the rate,
 - (c) specific accelerative "peri effects" of an azine-nitrogen (and of certain substituents) analogous to all the effects of an adjacent azine-nitrogen (and to all the "ortho effects" of substituents) are expected on the basis of those already observed; the accelerative "peri effects" apply to aminations and acid-catalyzed reactions rather than to alkoxylation,
 - (d) there is a marked difference in the activation from the possible resonance-activating positions, the reactivity in the 2,6-, 2,8- and 1,7-orientations with transition states and intermediate complexes of the *para,para*- (340) and *para,ortho*-quinoid types (341 and 344) being 10-100 times as great as the reactivity in the isomeric 1,5-orientation which has the *ortho,ortho*-quinoid resonance structure (345); the latter produces only about the same order of magnitude of reactivity as internuclear⁵⁹⁷ inductive activation of the 5-chloroisoquinoline type and *less* than intranuclear inductive activation⁵⁹⁷ of the 3-chloroquinoline type; this striking difference between the two conjugating positions (1,5- and 1,7-orientations) in the adjoining ring is a general phenomenon, which also occurs in electronic absorption spectra and in base-strengthening resonance of aminoazine cations.
- (4) Quaternization, acid catalysis, *N*-oxidation, and presumably hydrogen bonding to an azine-nitrogen increase the reactivity and in general alter the relative reactivity of rings and ring-positions. Greater activity of azinium compounds with anions is expected at the *ortho*-position when there is a large increase in the *entropy* of activation from electrostatic attraction as in the case of the *N*-methylpyridinium reactions (Table II, p. 270), but no kinetic data on bicyclics are available. With uncharged nucleophiles, reaction adjacent to the cationic center is unfavorable due to electrostatic repulsion in the transition state; in organic preparations (Section IV, B) the reactive position varies with the nature of the nucleophile perhaps due to a variation in the significance of the entropy of activation.

At the end of this section, a useful summation of bicyclic reactivity is given by means of the "activation-numbering system."

Cationization of an azine-nitrogen in polyazanaphthalenes offers many potential variations in the relative reactivity of the two rings and of the ring-positions. In reversible cationization, a minor cationized form may activate a leaving group more than does the major form if the former can stabilize charge by resonance rather than by induction or by a lower-energy resonance structure. Cationization can arise from quaternization, protonation, *N*-oxidation, or hydrogen bonding to an azine-nitrogen lone-pair. Its occurrence will vary with the number and orientation of the ring-nitrogens and the nature and position of the substituents. Therefore, to evaluate the reactivity of polyazanaphthalenes, it is necessary to know which nitrogens are the most electrophilic as well as to understand internuclear activation.⁵⁹⁷ In aminations in liquid amines or in hydrocarbon solvents, hydrogen bonding of the reagent to an azine-nitrogen will increase the relative reactivity of the adjacent position. The first kinetic study (Table XI, p. 338) of nucleophilic substitution of an *N*-oxide demonstrates substantial acceleration (10–30-fold) due to *N*-oxidation and activation somewhat *greater* than that in the nitronaphthyl analog. It is likely that a hydrogen-bonded solvate or hydrate of the *N*-oxide is involved here and in other studies of *N*-oxides unless special precautions are taken. In reactions of anions with quaternary pyridine compounds (Table II, p. 270), the entropy of activation increases with the proximity of the reacting ring-carbon to the quaternary center. This effect would be expected to accelerate reaction of **337**, relative to **338**, with anions, independent of differences in activation. The kinetic parameters for the reactions of quinolinium and isoquinolinium compounds (Section IV, B, 2) are unknown, and kinetic control of product formation has not been established. Kinetic studies in which the extent of hydrogen bonding to an azine-nitrogen is measured or is kept constant for each azine should shed light on this possible source of variations in the kinetic parameters.

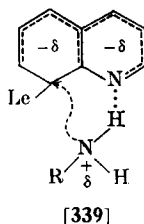


[337]



[338]

"*Peri effects*" of azine-nitrogens and of nitro groups are indicated by the data in Section IV, A, 2. For reaction in piperidine solution, the rates of *peri* or 1,8-situations of the leaving group and inductive-activating center are anomalously higher than those of the isomeric 1,3 analogs, the intervening distance in both being the same. This higher reactivity is postulated to be due to hydrogen bonding of the reagent (and possibly electrostatic attraction) in the transition state (339) or to solvent-mediated proton removal (cf. 235). In the case of



8-haloquinolines, the higher rate relative to that of the 3-isomer is primarily the result of a higher entropy of activation (Table X, p. 336). In such aminations, hydrogen bonding of the reagent to the azine-nitrogen in the ground state can also contribute to the rate and entropy effects. In alcoholysis of chloroazines, hydrogen bonding of the conjugate acid of the nucleophile to an azine-nitrogen or its protonated form should accelerate reaction of *peri* compounds. However, reaction in a solvent strongly hydrogen bonded to an azine-nitrogen can be somewhat decelerated by steric hindrance. Bifunctional nucleophiles can react via hydrogen-bonded *peri* transition states such as 339, and reversible interaction (cf. 245) with an electrophilic center in a reagent (e.g., hydroxyketones) can facilitate the reaction of *peri* compounds. All the accelerative "ortho effects" of substituents discussed in Sections I, D, 2 and II, E can operate similarly in *peri* compounds (e.g., *peri* NO₂ or CO₂⁻ with amine nucleophiles, or *peri* CONH₂ with alkoxides and other nucleophiles having an *extra* lone-pair). With negatively charged *peri* substituents, electrostatic repulsion of anionic nucleophiles can occur.

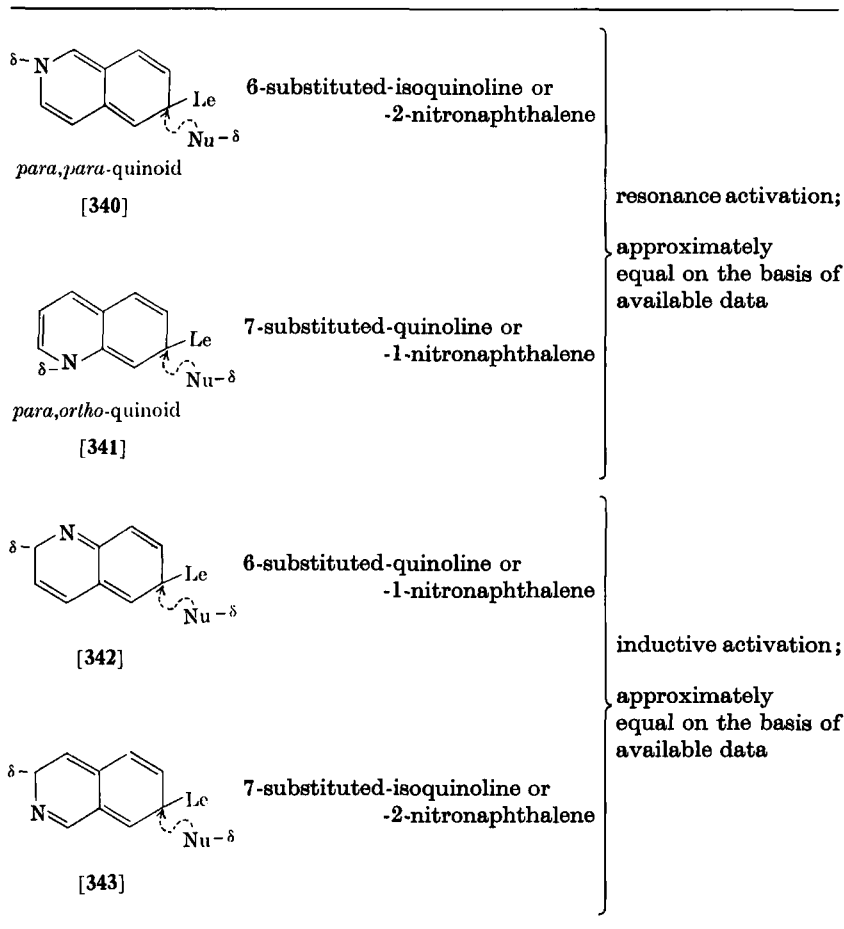
When a hydrogen atom is *peri* to an azine-nitrogen, there is no steric inhibition of resonance activation as there is in 1-nitronaphthalene^{600a} (4-methoxy-dechlorination of its 4-chloro derivative seems to be thereby decelerated only 2-fold in rate). Steric hindrance of nucleophilic substitution by the co-planar *peri* hydrogen is sometimes

considered likely,^{15, 600b} but there is experimental evidence⁴⁸⁷ (Section IV, A, 2) against it in naphthalenes and monoazanaphthalenes. Also, molecular models demonstrate that considerable bulkiness of the nucleophile or the substituent is necessary for steric hindrance to occur because of the non-coplanarity of the nucleophile and leaving group in the transition state and intermediate complex. If a bulky *peri* substituent hindered co-planarity of the leaving group in the ground state, reaction with small nucleophiles, at least, should be somewhat *accelerated*.

The information on *intranuclear*⁵⁹⁷ and *internuclear activations*⁵⁹⁷ in bicyclic azines and nitronaphthalenes is summarized here. In the transition states for azanaphthalenes and their nitronaphthyl analogs illustrated in Schemes II–IV, the leaving group position is kept constant in each comparison and it is assigned *either the 2- or the 4-position only*, for reasons discussed under the “activation-numbering system” later in this subsection.

Inductive activation (Scheme II) gives only about one-twentieth as great a rate increase as resonance activation from the adjoining ring. The pertinence of the *para,para*-quinoid structures (**342** and **343**) or their *para,ortho*-isomers (not shown) to the observed inductive activation depends on the relative significance of the field and mesomeric factors^{180, 344} in these inductive effects. The large decrease in effectiveness of internuclear resonance activation suggests that the internuclear mesomeric factor or resonance parameter^{179, 345} for bicyclic compounds is negligible, but further investigation would be desirable. If the energy of the resonance structures stabilized by induction was important, rather than the distance apart in space, then 4-substituted-isoquinolines (**350**) or -2-nitronaphthalenes would be more reactive than 3-substituted quinolines (**351**) or -1-nitronaphthalenes since there are four normal bond structures for **350** with the charge stabilized on carbon while, for **351**, two of the structures are higher-energy forms. In the only comparison available, the pair of bromo-nitronaphthalenes is aminated at about the same rate (Tables XII and XIII, pp. 342 and 345). No data are available on the inductively activated 5- or 8-substituted isoquinolines (**347** or **344**) or the analogous 2-nitronaphthalenes. The 5-substituted-isoquinolines (**347**) or -2-nitronaphthalenes would be expected to react about half as fast as the 8-substituted-quinolines (**346**) or -1-nitronaphthalenes, in proportion to the increased distance (ca. twice as great) in space between the activating center and the leaving group. The inductive effect falls off

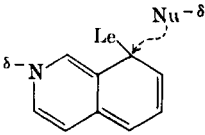
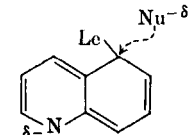
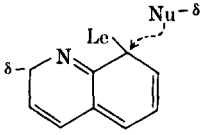
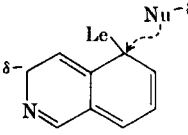
SCHEME II. Internuclear Activation in "2-Substituted (Le) 5-, 6-, 7-, and 8-" Azanaphthalenes and in the Nitronaphthalene Analogs



approximately inversely with increased distance in space in aromatic systems.^{180, 344, 601} Inductive activation, regardless of the nature of its σ -bond or field effect, is considered herein to arise primarily from inductive stabilization of the resonating negative charge in the transition state.

Resonance activation in the 8-substituted-isoquinolines (344) or -2-nitronaphthalenes is predicted to be greater than that in 5-substituted-quinolines (345) or -1-nitronaphthalenes due to the lower energy charge-

SCHEME III. Internuclear Activation in "4-Substituted (Le) 5-, 6-, 7-, and 8-" Azanaphthalenes and in the Nitronaphthalene Analogs

 <p><i>ortho,para</i>-quinoid [344]</p>	8-substituted-isoquinoline or -2-nitronaphthalene	resonance activation; no comparative data available
 <p><i>ortho,ortho</i>-quinoid [345]</p>	5-substituted-quinoline or -1-nitronaphthalene	
 <p>[346]</p>	8-substituted-quinoline or -1-nitronaphthalene	inductive activation; no comparative data available
 <p>[347]</p>	5-substituted-isoquinoline or -2-nitronaphthalene	

stabilization in the *ortho,para*-quinoid transition state (344) of the former. Resonance activation in the 5-substituted-quinoline (345) is *less* than inductive activation in the 8-substituted-quinoline (346) by about 15-fold as reflected in the rate of *piperidino*-dehalogenation.

This unusual relationship arises from the fact that both the 5- and 8-substituted-quinolines are anomalous. Reactions of the latter (346) are accelerated by the specific *peri* effects mentioned above. The reactivity of the former is low due to the relatively high energy of the *ortho,ortho*-quinoid transition state (345). This poor resonance activation in the 1,5-(or 4,8)-orientation has been observed in semi-quantitative comparisons of aminations of halonitronaphthalenes^{600b, 602} and reactions of hydroxide with azidonitronaphthalenes⁶⁰³; some activation is demonstrated here^{600b} and in kinetic studies below. The relation of resonance stabilization in *para,para*-quinoid (340) and *para,ortho*-quinoid structures (341) is known only for the nitro analogs which exhibit equal rates of piperidination. The effect of greater dispersal of the negative charge in space in the transition state is presumed to be negligible when the position of reaction is in an adjoining carbocyclic ring since electrostatic repulsion decreases with the inverse square of the distance.

The kinetic data for the structures in Schemes II and III lead to the following relationships of the rates of piperidino-dehalogenation (type of activation given in parentheses; ind. = inductive activation, res. = resonance activation):

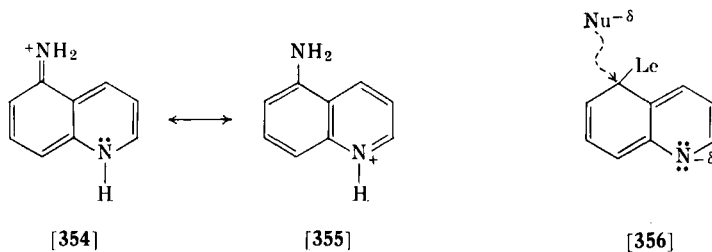
for quinolines,	8- (ind.) > 7- (res.) > 6- (ind.) > 5- Le (res.)
for 1-nitronaphthalenes,	7- (res.) > 8- (ind.) > 6- (ind.) > 5- Le (res.)
for 2-nitronaphthalenes,	6- (res.) > 7- Le (ind.)

In 8-substituted quinolines (346), the distance between the leaving group and the activating center is about one-half that in the 6-isomers (342). This difference plus the "*peri* effect" makes the former more reactive (3–5-fold). The "equidistant" 5- and 7-substituted-isoquinolines (347 and 343) and 6-substituted-quinolines (342) should be equally activated by induction; their nitro analogs also form an equivalent group. The difference in the rate between the resonance-activated 5- and 7-substituted-quinolines (345 and 341) is 10-fold and between the analogous 1-nitronaphthalenes it is 100-fold. This general discussion of relative activation is based on rate ratios corrected for the 2-fold differences between those of α - and β -naphthyl analogs. Some of the observed differences are small but are tentatively considered valid since they fit into a general relation supported by other data.

The reduction in rate of nucleophilic substitution *when the resonance-activating center is transferred to the adjoining ring* is 10^5 – 10^6 -fold for

quinolines, 10^2 – 10^3 -fold for 1-nitronaphthalenes, 10^5 -fold for 2-nitronaphthalenes, and 10^6 -fold (estimated) for isoquinolines. Similarly, increased length of the π -electron system produces⁶⁰⁴ a sharp decrease in conjugative interaction between 4-amino and 4'-nitro groups in phenyl, biphenyl, stilbene, etc. derivatives. In addition to the increased length when activation toward nucleophilic substitution is from the adjoining ring, there is an important increase in the energies of the most important resonance structures of the transition states. There is only one normal bond structure for the most important resonance contributors, those stabilizing a negative charge on nitrogen, when it is in the adjoining ring (**340**, **341**, **344**, and **345**). In contrast, there are two benzenoid bond structures when the azine-nitrogen is in the same ring (**348**, **349**, **353**; **352** is discussed below). For the reactivity of bicyclic azines with nucleophiles, a *single* transmission or attenuation factor^{599,605} has been misleadingly indicated as adequate. However, a different transmission factor needs to be defined for resonance activation and for inductive activation and, when given numerical values, the factors need to be clearly designated as applying to the rate, to the change in activation energy, or to the change in the σ -constant. The inductive effect is the same in compound **346** as in **350** and **351** but is decreased in **342**, **343**, and **347** by a small factor in the reaction rate, while resonance activation is decreased by a very large factor which varies with the orientation of activating center and leaving group. Resonance activation by a nitrogen atom or nitro group in the adjoining ring nevertheless accelerates the reaction rate up to 10^3 -fold. Generalizations^{606,607} to the effect that activation by a ring-nitrogen is not relayed to the adjoining ring are therefore not justified. In the pentadienyl carb-anions¹⁶⁶ from hexahydronaphthalenes, Bates *et al.* have found the U-shaped intranuclear anions to be more stable than the internuclear W-shaped form or the two internuclear "sickle-shaped" forms.

In the absence of sufficient data on nucleophilic substitution, certain predictions are made partly on the basis of the base-strengthening of amino groups in various positions in azines. These basicities depend primarily on the resonance energies of the aminoazine cations which generally bear the proton on the ring-nitrogen (**354**, **355**). Although binding of the proton is a thermodynamically controlled equilibrium process, both nucleophilic substitution (**356**) and base-strengthening (**354**) involve donation of a pair of electrons to a resonating system and its stabilization therein. The relative energies



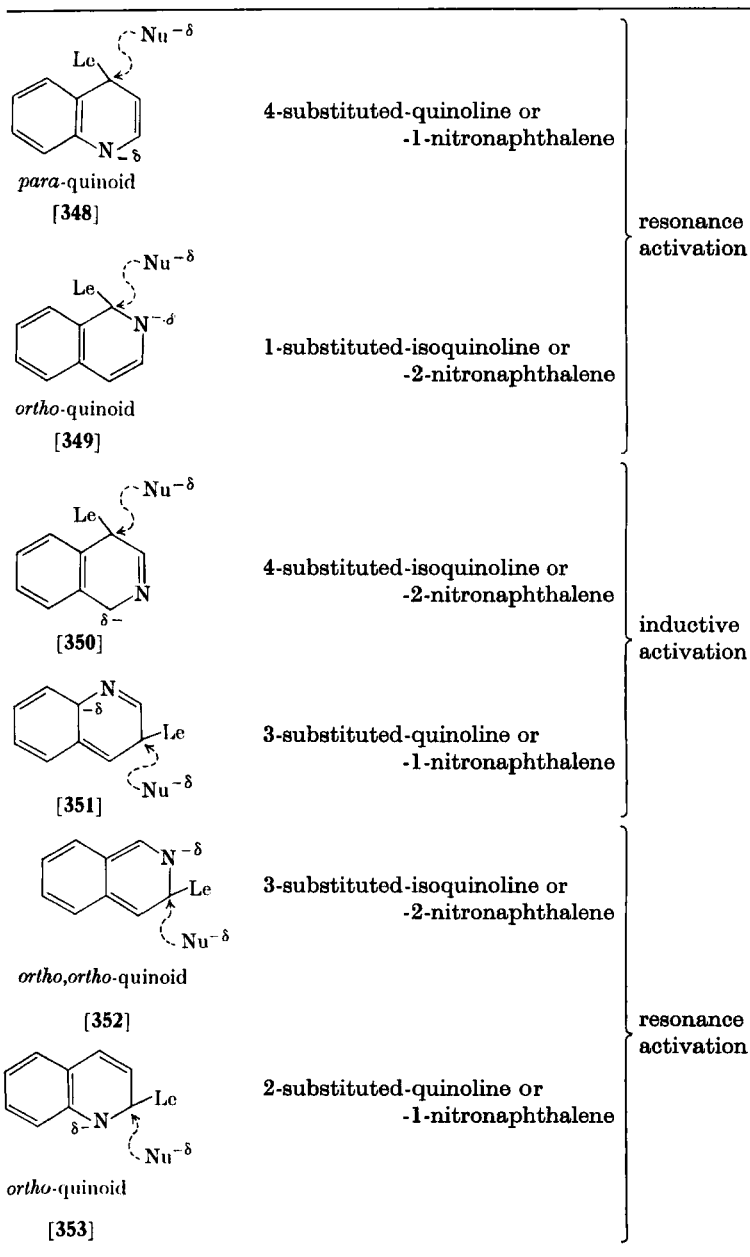
of the anionic and cationic resonance structures are necessarily similar. Where there are data on both, the correlation of reactivity toward nucleophiles is striking as is shown by the following base-strengthening relationships^{174, 175, 608}:

amino-quinolines	7 > 6 = 5 \cong unsubstituted
amino-acridines	3 > 2 = 1 \cong unsubstituted (<i>Chem. Abstr.</i> numbering) (3- and 1-derivatives are analogous to 7- and 5-substituted quinolines, respectively)
amino-quinazolines	7 \gg 5 = unsubstituted \cong 6
amino-isoquinolines	8 = 6 > 7 > 5 \cong unsubstituted

The *peri* derivatives, 1-aminoacridine, 8-aminoquinoline, and 8-aminoquinazoline, are anomalous.^{174, 175, 608, 609} This correlation for derivatives in the adjoining ring is free from the field effect or charge repulsion which can contribute to the relatively low base-strengthening in 2-aminoazines. The lack of interaction of a 1-aza moiety with the 5-position was noted¹⁷⁵ in the infrared study of 5-amino derivatives of quinoline, cinnoline, and quinazoline and of the analogous 4-aminoacridine. A corresponding difference in mesomeric interaction was also observed in the electronic^{610a} and infrared^{610b} absorption spectra of nitronaphthylamines. Therefore, it seems reasonable to expect poor resonance activation in the 1,5- or 4,8-relation (345) as a general rule in mono- and poly-azanaphthalenes, pending additional investigation. This effect is involved in the poorer reactivity of 5-fluoroquinoline *N*-oxide with nucleophiles relative to its 7-fluoro isomer.^{255b}

In Scheme IV, *intranuclear activation* is depicted. Kinetic studies with ionic nucleophiles show a variable relationship between the rates of reaction *ortho* and *para* to an azine-nitrogen (348 vs. 353 or 349) or nitro group due to entropy effects; the energy of activation is expected on further study to be consistently lower for the *para*-position. The relative reactivity of 2- and 4-substituted bicyclic azines

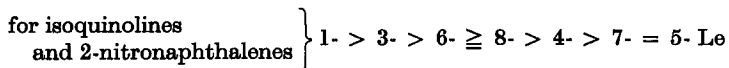
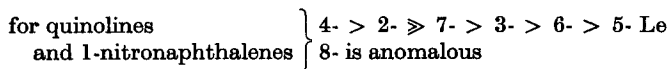
SCHEME IV. Intranuclear Activation in "4-Substituted (Le) 1-, 2-, and 3-" Azanaphthalenes, in "2-Substituted (Le) 1-, 3-, and 4-" Azanaphthalenes and in the Nitronaphthalene Analogs



involves the relative activation by *ortho* and *para* azine-nitrogens and, in the *ortho* case, charge repulsion and electron repulsion by the azine lone-pair (spatial requirement variously estimated^{188-191e} as negligible, like hydrogen, or like methyl). It also involves the relative reactivity of the β - and α -naphthyl analogs adjusted to the appropriate reaction temperature. The later work⁶¹¹ on naphthalene derivatives indicates that the energies of activation for α - and β -piperidino-dehalogenation are the same and thus the relative rate of reaction will not change with temperature, in contrast to the results reported in an earlier paper.⁶¹² The small difference found between the rates for α - and β -naphthyl compounds should be of diminishing significance as the number of ring-nitrogens increases. Aminations go faster with *ortho* than with *para* azines and nitro compounds due to electrostatic attraction or stabilization of the zwitterionic transition state by hydrogen bonding—a general rule for both types of compounds. The lower energy of *para* compared to *ortho* transition states is discussed in Section II, B and is supported by a similar difference in the electronic absorption spectra⁶¹³ of substituted azines and in the basicity⁶¹⁴ of monocyclic and bicyclic azine derivatives (alkoxy, alkylthio, amino, alkylamino, dialkylamino) and *N*-alkylazinones. The relation of the resonance energies of the cations of these derivatives is comparable to that of the anionic transition state and intermediate complex of nucleophilic substitution, and, in both cases, electrostatic repulsion is greater in *ortho*- than in *para*-substituted derivatives. The general relationship of the reactivity of the azines and naphthalenes in Scheme IV is:

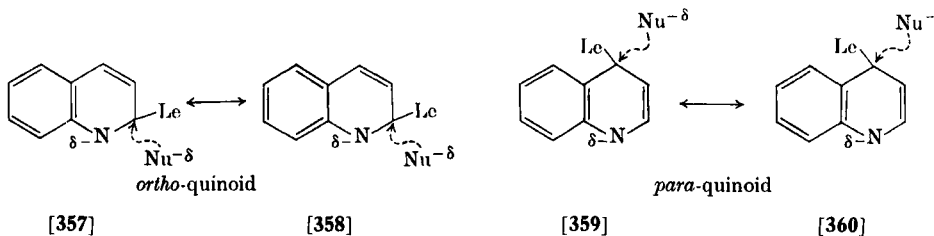


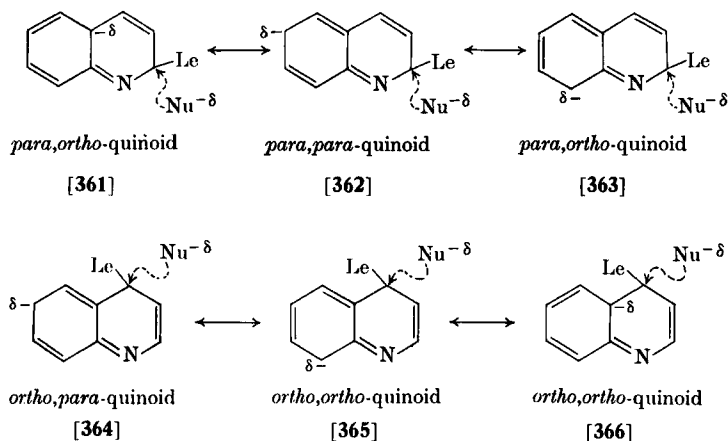
where the type of activation is given in brackets (res. = resonance activation, ind. = inductive activation). The difference between the resonance-activated isomers **349** and **352** is enormous (10^5 -fold), but the less reactive **352** is still 10–100 times as reactive as the inductively activated **350** and **351**. Two general relationships of reactivity are derived from experimental results. These relationships can be



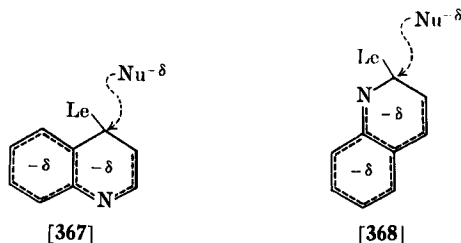
applied also to the activating and deactivating effects of substituents. Confirmation of these relationships is needed not only for understanding quinoline and isoquinoline chemistry but for providing the foundation for interpreting the reactivity of bicyclic polyazines.

Benzo-fusion onto an azine usually activates it toward nucleophilic substitution, but a 2,3-orientation (cf. 352) of the leaving group and azine-nitrogen (or activating substituent) has special characteristics which are discussed below. Additional benzo-fusion onto quinoline and isoquinoline to form acridine and phenanthridine gives further activation.^{55, 615} The process of nucleophilic substitution of bicyclics compared to monocyclics has been presumed⁴⁸⁷ to involve a smaller loss of resonance energy, and this is supported by molecular orbital calculations (based on the intermediate complex structure for the transition state).⁶¹⁶ In the transition state, the benzo-ring accelerates reaction by accomplishing part of the negative charge stabilization and producing a nine-atom resonating system (such as 367 and 368) having less energy than the five-atom system (276) of monocyclics. Reactivity at different positions in bicyclic azines is due to the combination of (a) the factors in monocyclic azine reactivity (Sections II, B and III, A), (b) resonance stabilization in the reacting ring, and (c) resonance stabilization in the adjoining ring, as shown for 2- and 4-substitution of quinoline (357 to 366). The structures (357 to 360) involving factor *b* favor 4-substitution via *para*-quinoid structures while those (361 to 366) involving factor *c* favor 2-substitution via structures having a more *para*-quinoid nature. The 2-substituted quinoline transition state has been presumed,⁶¹⁷ when written as 357 and 358, to be more extensively conjugated or to "interfere less with benzene ring aromaticity" than does that of the 4-analog (359 and 360). However, the pentadienoid and benzenoid systems 367 and 368 are fused into a single resonating system in which the point of fusion and the location of greatest charge stabilization (ring-nitrogen) are merely transposed with respect to the reaction site. The presumed



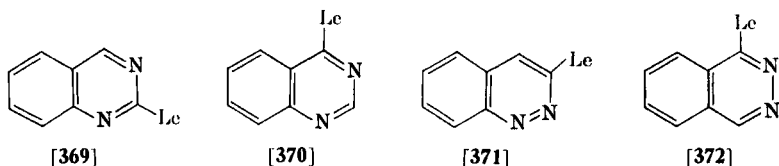


difference in energy should favor 2-chloro- over 4-chloroquinazoline and favor 4-chlorocinnoline over 2-chloroquinoxaline, but, in both comparisons, the 4-substituted azine is the more reactive. Furthermore, the supposedly greater reactivity of 2-substituted quinolines is not borne out by the three reactions with anions on which there is kinetic data. For 1-substitution of isoquinoline, the structures



involving factor *b* are isomers of **357** and **358** and those involving factor *c* are isomers of **364–366**, each with the ring-nitrogen transposed. Comparison of these resonance structures suggests that 1-chloro-isoquinoline should be less reactive than 2-chloroquinoline, but it is somewhat more reactive. To evaluate the significant factors involved, 1-chloroisoquinoline, 2- and 4-chloroquinolines, and their internuclear resonance-activated isomers should receive further study. For 3-chloroisoquinoline, the structures involving factor *c* are as favorable toward reaction as for 2-chloroquinoline, but those involving the more important factor *b* are not.

The 2,3-orientation of an azine-nitrogen and a leaving group is characterized by activation which is exceptionally poor compared to other resonance activations. The poor activation, which is often grossly underrated,^{55, 618} is still substantial relative to the substituted naphthalene: 10^3 – 10^5 -fold increase in the rates of alkoxylation and of alkylamination. The properties of 2,3-orientation come into play in all 3-substituted naphthalenes or azanaphthalenes which bear an azine-nitrogen or activating substituent in the 2-position (Section IV, A, 2). This orientation is subject to such a decrease in activation due to the relatively poor stabilization of charge in the *ortho,ortho*-quinoid structure (352) that 3-substituted isoquinolines and 2-nitronaphthalenes⁶⁰² are *less reactive* than 2-substituted pyridines and nitrobenzenes (Section IV, A, 2). Insertion of a 3-aza moiety into a 2-substituted quinoline to give a 2-substituted quinazoline (369) produces only a relatively small increase in the reactivity; as a result, it is similar in reactivity to the inductively analogous 2-substituted quinoxaline (1,4-diazanaphthalene). Due to the absence of the "2,3-effect," the insertion of a second ring-nitrogen into a 4-substituted quinoline at the 3-position produces a very large activation in 370. Similarly, the effect of inserting a ring-nitrogen into a 3-substituted quinoline to form 3-substituted cinnoline (371) is less than insertion into a 4-substituted isoquinoline to give a 1-substituted phthalazine (372) due to the creation of the very poorly activating 2,3-orientation in the former. The relation of 2,3-activation to internuclear resonance activation (2,6-, 2,8-, 1,7-, or 1,5-orientations) needs further study since the only available comparison is piperidino-debromination of nitronaphthalenes. Although hydrogen bonding in the transition state accelerates reaction of the 2-nitro-3-bromo compound, probably only a small part of the 15-fold superiority in rate is due to this effect.



The *irregularity in the bond lengths of naphthalene in the ground state* (misleadingly called bond fixation) has been used to explain the "poor transmission"^{55, 619–621} of resonance activation in 2,3-orientations of an azine-nitrogen and a leaving group. This explanation is

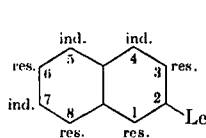
based on the retention of the 2,3-single-bond *during the reaction* rather than on the influence of the bicyclic system on charge stabilization in the transition state. Naphthalene by theoretical calculations^{622, 623} does have bond-length irregularities (1,2-bond order of 1.67; 2,3-bond order of 1.33) which are confirmed, but shown to be of somewhat smaller magnitude, by X-ray crystallography.^{624, 625} The 2,3-bond is therefore close to being a double bond in the ground state of naphthalene (resonating system with a π -electron density of unity at every position^{626, 627}). Naphthalene itself in reacting with a nucleophile (e.g., H_2N^-) reaches the α - and β -transition states in amounts dependent upon their respective free energies. Since there is only one ground state energy, the difference in reactivity is determined by the relationship of the transition state energies, not by the small irregularities of bond length. It seems clear from consideration of the transition states that stabilization of charge in the 2,3-arrangement (349) in bicyclics would be poorer than in isomeric arrangements (349 and 353) *even if all the bonds in naphthalene had the same length*. For the transition state stabilizing charge at the 3-position of a 2-aza bicyclic compound, only one normal bond structure (352) can be written in contrast to the transition state for the 1-position (349) (here there would be two different ground states with a slight difference in their energies). The large difference in reactivity is attributed to the higher energy of this *ortho,ortho*-quinoid structure (352) and is also indicated in studies of the basicity and spectral properties mentioned above. Interpretation of dipole moments^{621, 628} and theoretical calculations¹² arrive at the conclusion that bicyclic azines have small double-bond irregularities (e.g., 1,2-bond order of 1.58 and 2,3-bond order of 1.47 in isoquinoline) in the ground state similar to those in naphthalene. However, a difference in the ability to achieve low energy stabilization of the negative charge donated by the nucleophile is the key to the relative reactivity in bicyclic as well as in monocyclic azines.

Theoretical calculations correctly predict poor resonance stabilization of charge in the 2,3-orientation (Section IV, A, 2) but give variable predictions as to the relative reactivity of the 1,4- and 1,2-orientations and incorrect predictions of the activation from the adjoining ring. Therefore, in their present forms, they are not a reliable guide to the reactivity of bicyclic azines with nucleophiles. Reactivity of bicyclic azines and azinium compounds has been approached theoretically by calculating the electron distribution^{15, 605, 629, 630} in the ground state and also by estimating the localization energies or the lowering of

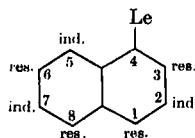
activation energy due to differences in the resonance energy in the transition state^{12, 17, 631} (the intermediate complex was taken as its structure). As shown for monocyclics, the former method gives various erroneous predictions.^{15, 629, 630, 632} The latter is qualitatively correct for only a restricted range of compounds⁵⁵ and suffers from the following shortcomings: (1) it does not take into account inductive activation in either ring, (2) it incorrectly predicts equal resonance activation from the two possible positions in the adjoining ring, (3) it assumes constancy of entropy of activation and of solvation energies, and (4) it assumes absence of hydrogen bonding to an azine-nitrogen in the ground and transition states and absence of hydrogen bonding or of electrostatic interactions in the transition state. Chapman and Russell-Hill⁵⁵ prefer piperidine as a nucleophile in studies evaluating the Longuet-Higgins molecular orbital treatment¹⁷ since the variation of the entropies of activation is comparatively small. On the other hand, the reactions of ethoxide ion show a wide range of ΔS^\ddagger values within each class of activation, and the theory is therefore considered⁵⁵ inapplicable. When ΔS^\ddagger is not constant, the heats of activation at absolute zero are more closely related to the logarithm of the reaction rate at ordinary temperatures than to the experimental heats of activation, according to Evans and Polanyi.⁶³³ Some, but far from all, of the ethoxylation rates of bicyclic azines fit a straight-line relation with the *calculated* heats of activation.⁵⁵ The general question of whether the heat of activation or the reaction rate is the better measure of activation by an azine-nitrogen seems to warrant further study. As Ridd^{634a} has pointed out, the calculated localization energies grossly underestimate the activation by an azine-nitrogen: a rate increase of about 10^4 -fold for 2-chloroquinoline compared to 2-chloronaphthalene is predicted, while 10^{10} -fold and 10^6 -fold increases in the rates of ethoxylation and piperidination are observed (cf. Section IV, A, 2). The difference in the reactivity and in the activation energy between α - and β -naphthyl compounds is grossly overestimated^{634b} by these calculations. π -Electron distribution in the ground state is believed to be more pertinent in attack by strong nucleophiles and localization energies more pertinent in attack by weak nucleophiles.^{133, 629, 635} However, there seems to be no experimental data supporting this belief. The limitations of theoretical calculations of heteroaromatic reactivity have been summarized recently by Ridd.^{634b}

The uses of an *activation-numbering system for bicyclic compounds* will be presented and the generalizations summarizing the reactivity

of bicyclic azines will be restated by means of it. The *Ring Index* and *Chemical Abstracts'* fused-ring nomenclature is bewildering when one tries to compare 74 possible bicyclic azines with 254 *different* ring-positions. Pyrazino[2,3-*d*]pyrimidine can bear a leaving group at positions 2, 4, 6, or 7, and the isomeric pyridazino[4,3-*c*]pyridazine can be substituted at the 3-, 4-, 7-, or 8-positions. Some indication of the relation of the leaving group to the ring-nitrogens and of the latter to each other is afforded by the azanaphthalene nomenclature: 1,3,5,8-tetraazanaphthalene and 1,2,5,6-tetraazanaphthalene, respectively. In both systems of nomenclature, the numbering varies with the point of fusion and the leaving group can bear any number from 1 to 8. Obviously, no systematic nomenclature could be expected to be in accord with the reactivity of bicyclic azines, so an activation-numbering system is proposed. In bicyclic azines, as in naphthalene, there are only two spatially different positions for the leaving group to occupy,



[373]



[374]

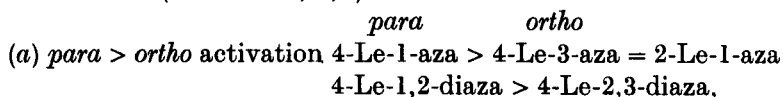
and, in this numbering system, the leaving group is assigned only the 2- or the 4-position. The result is a *single* pattern of activation by the ring-nitrogens from the various positions: in both structures **373** and **374**, a nitrogen atom in any one or all of the 1-, 3-, 6-, and 8-positions activates by resonance (res.), and in any one or all of the 2-, 4-, 5-, and 7-positions it activates by induction (ind.). If the locations of the ring-nitrogens are designated by the azanaphthalene system, it becomes clear *just from the name* whether a particular compound is activated by resonance or induction or both and whether activation is intranuclear or internuclear, e.g., "2-chloro-4,7-diazanaphthalene" (induction) and "2-chloro-6,8-diazanaphthalene" (intranuclear resonance). The shift of the ring-nitrogens and the resulting change in activation are apparent. A similar difference in the activation between 2-chloropyrimido[5,4-*d*]pyrimidine and 2-chloropyrimido[4,5-*d*]pyrimidine is easily recognized from the names 2-chloro-1,3,5,7-tetraaza- and 2-chloro-1,3,6,8-tetraaza-naphthalene. When the numbering is unconventional, quotation marks can be used, but it should be emphasized that this special numbering system will not give an erroneous

or confusing designation of structure. An additional advantage of this activation numbering system, devised here for nucleophilic substitutions, is that the resonance and inductive effects of activating and deactivating substituents on nucleophilic substitution fit the same pattern. It will also be recognized that electrophilic substitution can be related to the same pattern of conjugative and inductive electron donation.

Since this numbering system gives the *activation pattern* of the ring system in relation to the leaving group, one can compare the reactivity of different positions in the same azine; e.g., the three β -naphthyl-like positions in 1,6-naphthyridine are related as 2-chloro-1,6-diaza-, "2-chloro-4,7-diaza," and "2-chloro-3,8-diaza" analogs. The reason for not carrying over the α - and β -naphthalene designation and numbering the leaving groups as 1 and 2 is that two sets of activation relationships would be necessary.

Although comparison in polyaza compounds is facilitated most by this method of numbering, reactivity relations in monoazanaphthalenes are also clarified, e.g., between 4-chloroquinoline and 1-chloroisoquinoline (1-aza- and 3-aza-4-chloro analogs) and among the 14 possible monoaza derivatives of **373** and **374**. The difference between 2-chloropteridine (2-chloro-1,3,5,8-tetraazanaphthalene) and 6-chloropyrimido[5,4-*c*]pyridazine (2-chloro-1,3,5,6-tetraazanaphthalene) is seen to be a shift of a single nitrogen atom from one internuclear resonance-activating position to another position which, as reactivity data show, is equivalent. Activation in 2-chloropyrimido[4,5-*d*]pyridazine (2-chloro-1,3,6,7-tetraazanaphthalene) is seen to be equal to that in the 6-chloropyrimidopyridazine above since the only difference (5-aza vs. 7-aza) can be seen to involve ring-nitrogens having equal inductive effects.

This numbering system is especially useful since all the reactivity characteristics summarized above can be recognized just from the name of the compound. *Resonance activation* of the leaving group (Le) for alkoxylation or alkylamination has the following observed characteristics (Section IV, A, 2):



the magnitude of the difference varies substantially; with piperidine, the nature of the zwitterionic hydrogen-bonded transition state causes the reverse relation but only in quinoline;

- (b) 2-Le-3-aza gives poor activation, but greater than internuclear⁵⁹⁷ resonance activation and greater than inductive activation (intra- and inter-nuclear);
- (c) 2-Le-6-aza = 2-Le-8-aza = 4-Le-6-aza equally activated on the basis of the limited data available;
- (d) 4-Le-8-aza gives very poor activation which is much less than in 2-Le-8-aza, etc. and less than intranuclear induction⁵⁹⁷ (e.g., 3-Le-1-aza) but about equal to internuclear induction.

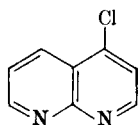
Inductive activation has been found to have the following characteristics:

- (a) 2-Le-4-aza = 4-Le-2-aza \leq 4-Le-5-aza(internuclear) all equidistant; accelerative "peri effects" in 4-Le-5-aza compounds occur in some reactions;
- (b) 2-Le-5-aza = 2-Le-7-aza = 4-Le-7-aza all equidistant;
- (c) group *a* increases the rate about twice as much as group *b*.

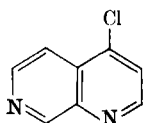
The special cases "2-Le-3-aza," "4-Le-8-aza," and "4-Le-5-aza" are apparent from a glance at the names of the polyaza compounds given to them by the activation-numbering system.

The relation of activation by *para* vs. *ortho* ring-nitrogen in bicyclics is altered by these special cases. For example, 4-chloroquinazoline (4-Cl-1,3-diaza) is much more reactive than the 2-chloro isomer (2-Cl-1,3-diaza) for two reasons, one being the poor activation in "2-Le-3-aza" compounds. 4-Chloro-1,8-naphthyridine will be decreased in reactivity relative to its 2-chloro isomer due to the very poor activation in 4-Le-8-aza compounds and it may be only slightly more reactive than the mono-aza analog 4-chloroquinoline. The greater reactivity at the 2-position of 2,4-dichloro-1,8-naphthyridine⁶³⁶ can be ascribed to this "4-Le-8-aza effect."

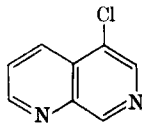
The relationships predicted by Chapman¹³⁹ differ from those presented here primarily as a result of his considering 2-Le-3-aza compounds as virtually unactivated and of not including the "4-Le-8-aza effect." For example, the series 4-Cl-1,6-diaza > 4-Cl-1,8-diaza (375) > "4-Cl-3,8-diaza" seems more realistic than considering them equal,¹³⁹ two factors obviously contributing to the 4-Cl-1,6-diaza > "4-Cl-3,8-diaza" relation. Differences in the group 4-Cl-1,5-diaza > 4-Cl-1,7-diaza (376) > "4-Cl-3,5-diaza" are expected since 376 is only slightly less activated than 375. "4-Chloro-2,8-diaza"-naphthalene (377) would be activated less by resonance and more by induction than 376 and only about equal to 378 due to the "4-Le-8-aza effect." "2-Chloro-3,5-diaza"-naphthalene should be greater than 377 but



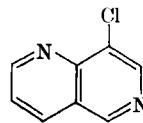
[375]



[376]



[377]

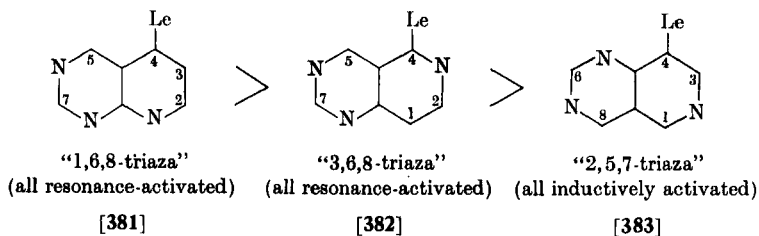


[378]

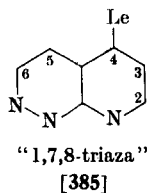
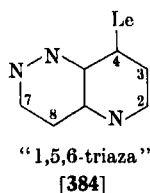
less than **376** in reactivity. We would rearrange Chapman's series and place 8-chlorocinnoline ("4-Cl-5,6-diaza") > 8-chloroquinazoline ("4-Cl-5,7-diaza") \geq 5-chlorocinnoline ("4-Cl-7,8-diaza") and in another series place 3-chlorocinnoline ("2-Cl-3,4-diaza") > 7-chloroquinazoline ("2-Cl-6,8-diaza") > 6-chlorophthalazine ("2-Cl-6,7-diaza") > 6-chloroquinazoline ("2-Cl-5,7-diaza").

The relations in Scheme V take into account intranuclear and internuclear resonance activation and the special cases of "2-Le-3-aza" (poor) and "4-Le-8-aza" (extremely poor) activation as well as the two groups of inductive activation; the possibility of an accelerative "peri effect" in substitutions with protic nucleophiles is indicated by the \geq sign for "4-Le-5-aza" compounds.

The relation **381** > **382** > **383** is arrived at by an extension of the observed reactivity characteristics to triazanaphthalenes. The poorly activating "4-Le-8-aza" relation in **385** and the greater inductive

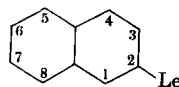


activation in **384** lead to the expected relation, **384** > **385**. In other 4-substituted triazanaphthalenes, one arrives at the relations 1,2,3- > 1,2,6- > 1,2,5- \geq 1,2,8- \geq 1,2,7-triaza and 1,3,6- > 1,3,5- = 1,2,3-



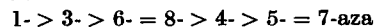
SCHEME V. Predicted Reactivity in Azanaphthalenes
(Using the Activation-Numbering System)

2-Substituted Compounds

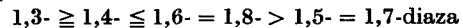


[379]

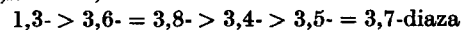
Monoazines



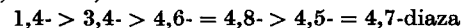
1,x-Diazines



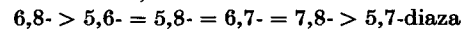
2,x- and 3,x-Diazines



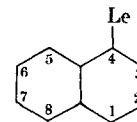
3,x- and 4,x-Diazines



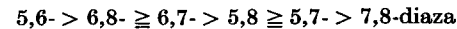
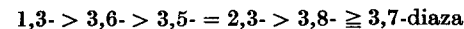
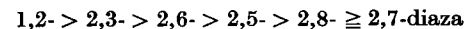
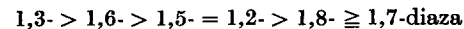
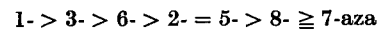
Benzodiazines, internuclear activations



4-Substituted Compounds

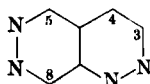
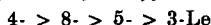


[380]

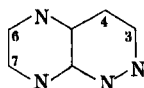
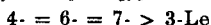


$\geq 1,3,8- \geq 1,3,7$ -triaza and for the 2-substituted isomers $1,3,6- = 1,3,8- > 1,3,4- > 1,3,5- = 1,3,7$ -triazanaphthalene. In various tetra-azanaphthalenes, the expected relation is $1,3,6,8- > "1,3,5,6-" = 1,3,5,8- = "1,3,7,8-" = 1,3,6,7- > 1,3,5,7$ -tetraaza for 2-substituted compounds and $"1,3,5,6-" \geq 1,3,6,8- = 1,3,6,7- > "1,3,7,8-" > 1,2,5,6- \geq 1,2,6,8- > 1,2,7,8-" \leq 1,2,5,7$ -tetraaza for 4-substituted derivatives. Due to the magnitude of the greater reactivity of 4- compared to 2-substituted quinazolines, it is reasonable to expect the same relation not only in "1,3,5,6-tetraaza"-naphthalenes but also in 1,3,6,8- and "1,3,7,8-tetraaza"-naphthalenes in spite of the opposing "4-Le-8-aza effect." The most reactive *carbocyclic* position in azanaphthalenes would be the 6-position in the unknown benzotetrazine system; this "2-Le-5,6,7,8-tetraaza" activation would be much less than that in 2-substituted quinoline, however.

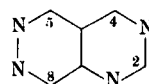
By similarly deducing the activation for each ring-position, the expected reactivity relationships shown with structures 386-388 can be derived.

Pyridazino[4,5-*c*]pyridazine

[386]

Pyrazino[2,3-*c*]pyridazine

[387]

Pyrimido[4,5-*d*]pyridazine

[388]

By means of the above tentative reactivity "rules" and the activation-numbering system, one can interpret the behavior described in Section IV,B and make additional predictions. In connection with the behavior of the polysubstituted compounds discussed in Section IV,B, it should be re-emphasized that their behavior gives an unreliable estimate of the relative reactivity at the different ring-positions. Two other cautions concerning the reactivity of bicyclic polyazines need to be kept in mind. One is the possibility that the increased hydrogen-bonding capacity and the resulting partial cationization will alter the relative reactivity or shift the reaction from one ring to another. The other is that the intervention of covalent adducts as substrates may easily go unrecognized. Nucleophilic substitution might take place *only* on a covalent-hydrated form (or an analogous type of adduct^{11b, 150}), which could revert to an aromatic structure due to the effect of the substitution elsewhere in the molecule or the nature of the isolation process. The reactivity would then be

determined by the properties of the covalent adduct (cf. pteridine in Section IV, B).

2. Kinetic Data on Nucleophilic Substitution of Bicyclic Azines and Nitronaphthalenes

To derive the maximum amount of information about intranuclear⁵⁹⁷ and internuclear activation⁵⁹⁷ for nucleophilic substitution of bicyclo-aromatics, the kinetic studies on quinolines and isoquinolines are related herein to those on halo-1- and -2-nitro-naphthalenes, and data on polyazanaphthalenes are compared with those on polynitronaphthalenes. The "reactivity rules" thereby deduced are based on such limited data, however, that they should be regarded as tentative and subject to confirmation or modification on the basis of further experimental study. In many cases, only a single reaction has been investigated. From the data in Tables IX to XVI, one can derive certain conclusions about the effects of the nucleophile, leaving group, other substituents, solvent, and comparison temperature, all of which are summarized at the end of this section.

The question of the occurrence of "cine" or aryne substitution in some of these reactions has been raised^{55,617} but not answered adequately. The "normal" product, 2-methoxynaphthalene was shown⁵⁵ to be formed from 2-chloronaphthalene and methoxide ion, and the "normal" 6- and 8-piperidinoquinolines were proved⁶¹⁷ to be products of piperidino-debromination of 6- and 8-bromoquinolines, all in *unspecified yield*. More highly activated compounds were then assumed not to react via the aryne mechanism. Even if the *major* product had been characterized, the occurrence of a substantial or predominant amount of aryne reaction may escape notice when strong orientation or steric effects³⁶ lead to formation of the "normal" displacement product from the aryne. A substantial amount of concurrent aryne reaction may also escape detection if it yields an amount of cine-substituted material easily removed in purification or if the entire reaction mixture is not chromatographed. Kauffman and Boettcher³⁵ have demonstrated that activated compounds such as 4-chloropyridine do indeed react partially via the aryne mechanism (Section I, C, 1).

An "abnormal" substitution, not detected with the other isomers, is the major reaction in attempted methoxy-debromination of 6- and 8-bromoquinolines. A 50–70% yield of unsubstituted quinoline was isolated.⁶³⁷

TABLE IX
HALONAPHTHALENES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTIONS

Line No.	Naphthalene substituents	Nucleophile (solvent)	Unimolecular rate constant ^a (temp. °C) 10 ⁶ k, sec ⁻¹	Activation energy ^b kcal mole ⁻¹	Frequency factor ^c log ₁₀ A	Ref.
1	1-Cl	piperidine (solvent ^d)	(234°) 1.86	25.4	7.7	611
2	1-Cl	piperidine (solvent ^d)	(165°) 0.041	—	—	612
3	1-Br	piperidine (solvent ^d)	(200°) 1.97	25.0	8.2(9.4) ^e	611 (612)
						642
4	1-Br	piperidine (H ₂ O)	(188°, 65 atm. ^f) 1.1	—	—	637
5	1-Br	MeO ⁻ (MeOH)	(174°, 65 atm. ^f) 8.6	—	—	637
6	1-I	piperidine (solvent ^d)	(200°) 3.36	23.1	8.8	612
7	2-Cl	piperidine (solvent ^d)	(233.5°) 1.39	23.1	6.7	611
8	2-Cl	piperidine (solvent ^d)	(165°) 0.052	—	—	612
9	2-Cl	EtO ⁻ (EtOH ^g)	[(20°) 9.1 × 10 ⁻¹¹] ^h	39	13 ^e	55, 139
10	2-Br	piperidine (solvent ^d)	(200°) 4.3	24.9(27.6)	8.5(11.0) ^e	611 (612)
						642
11	2-Br	piperidine (H ₂ O)	(186°, 65 atm. ^f) 1.3	—	—	637
12	2-Br	MeO ⁻ (MeOH)	(174°, 65 atm. ^f) 8.4	—	—	637
13	2-I	piperidine (solvent ^d)	(200°C) 4.75	24.6	9.6	612

^a Pseudo-unimolecular rate constants measured at various temperatures, one of which is tabulated.

^b The Arrhenius activation energy,⁴⁷⁹ E_A.

^c The Arrhenius frequency factor, ⁴⁷⁹ A, is in liter mole⁻¹ sec⁻¹.

^d Nucleophile used as reaction solvent.

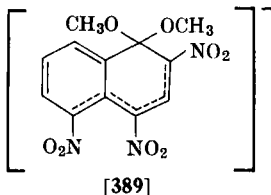
^e Entropy of activation,⁴⁸² ΔS[‡], in cal mole⁻¹ deg⁻¹ for line 3 is -39.8, for line 9 is -2.0, and for line 10 is -39.0⁶⁴² or -32.4;⁶¹² cf. difference in reported E_A values for the latter.

^f Atmospheres of pressure under which the reaction was carried out.

^g Water added to absolute ethanol to make 99.8% ethanol.

^h Bimolecular rate constant in liter mole⁻¹ sec⁻¹; a value of 10⁻¹² at 60° was given.¹³⁹

Irregular kinetics were observed in methoxy-dechlorination of 1-chloro-2,4,5-trinitronaphthalene. This observation was shown⁶³⁸ to arise from reaction of the 1-methoxy product with more methoxide ion to form the intermediate complex **389** comparable to that formed



from picryl chloride via methyl picrate. This complicating formation of "Meisenheimer complexes" (Section I, D, 1) can occur with any highly activated azine or carbocyclic compound which gives a substitution product still moderately reactive, especially toward strong nucleophiles.

Covalent addition of solvent or of nucleophile prior to substitution will alter the reactivity characteristics of the substrate. Covalent addition of nucleophile after substitution will affect the kinetics in a way similar to the formation of **389**. Covalent hydration and additions are especially likely to occur in bicyclic azines. (cf. Section IV, B, 3, b).^{11, 150, 151, 614}

The intervention of acid catalysis leads to irregular or third-order^{218, 475} kinetics in several instances involving alcoholysis,⁶³⁹ aminolysis,^{55, 639} or mercaptolysis⁶⁴⁰ (Table X, line 8). Small changes in the basicity of the substrate or of the amine produce large effects: 4-chloroquinoline, but not the less basic 2-chloro isomer, is susceptible to acid catalysis in amination with alcoholic piperidine; both 2- and 4-chloroquinoline show acid catalysis with the slightly less basic reagent, morpholine.⁵⁵ Some technical "problems," such as separation into two phases, actually gave uniform second-order rate constants due to the acid catalyst (amine salt) and substrate being in different phases, while the same reaction under homogeneous conditions showed irregular kinetics.^{617, 641} Regular kinetics may occur during a later part of a reaction after saturation with the acid catalyst is complete (e.g., the hydrochloride of the product of the reaction on line 8, Table X).⁶⁴⁰

The reactions were shown, in a representative number of cases, to follow second-order kinetics and to obey the Arrhenius law.⁴⁷⁹ The kinetic parameters are, of course, for the entire two-stage process.

The rate constants (in absolute solvents unless otherwise specified) are measured at a temperature giving a convenient reaction rate and calculated for a reference temperature used for comparison. These constants have all been converted to the same units and tabulated as 10^6k . Where comparisons could otherwise not be made, pseudo-unimolecular constants (Tables IX and XIII, and as footnoted in Tables X to XIV) are used. The reader is referred to the original articles for the specific limits of error and the rate equations used in the calculations. The usual limits of error were: for k , 1–2%; E_A or ΔH^\ddagger or ΔS^\ddagger , 2–5%; and $\log_{10} A$, 5%, with errors up to double these figures for some of the high-temperature reactions.

Brower^{637, 641} found that the reactions of halo-quinolines and -naphthalenes with piperidine or alkoxides are accelerated 2–5-fold by pressures up to 1,300 atmospheres. Thereby, he has studied the volume change of activation^{61b} resulting from the transformation of reactants into the transition state and found it to be highest where the reactivity is lowest (greatest polarization and charge development in the transition state and, therefore, greatest electrostriction of the solvent by the transition state). The interpretation of mechanistic details by this novel approach seems to be as difficult as it is by the usual kinetic approach. Brower concludes that the faster reactions involve transition states more nearly resembling the separate reactants and that the transition states for amination and alkoxylation are similar in nature.

The activation produced by the ring-nitrogens in bicyclic azines is based on the increase in reactivity over that in the corresponding naphthalenes. The difference in reactivity of 1- and 2-halo-naphthalenes (Table IX) toward piperidine^{611, 612, 641, 642} is slight; the relation of their kinetic parameters is not consistent.^{611, 612, 642} At 200°, the 2-halo derivatives react 0.8–2.2 times as fast as the 1-isomers. For the bromonaphthalenes, the rates with methoxide ion⁶³⁷ (174°) are the same, but with radioactive lithium bromide^{262b} (> 200°) in polyalkylene glycols, 2-bromonaphthalene reacts more rapidly. It has been noted^{612, 644} that the relation of the reactivity of the 1- and 2-positions in these high-temperature reactions (165°–250°) is not the same as that calculated for the 0–100° range (for comparison with more activated bicyclics). When the activation energy for the faster reaction is the higher one (e.g., Table IX, lines 1, 2, 7, and 8), the rate ratio at 235° (1.3/1) is reversed by even a small lowering of the reaction temperature (at 165°, 1/1.3). A similar reversal will occur with

the iodo derivatives (Table IX, lines 6 and 13), but Berliner's E_A values⁶¹² for the bromo derivatives have been disputed.⁶⁴² Wheland⁶⁴⁴ has noted the correlation of Berliner's activation energies with the *expected* greater reactivity at the 1-position. However, all the data now available put the expectation in doubt, in spite of the 1-amination (NaNH_2 in phenol, 220°) of naphthalene in 20% yield^{645a} and of the hydrolysis (160°) of 1- but not 2-naphthylsulfonic acid.^{645b}

Extending this comparison of reactivities of the 1- and 2-positions to nitronaphthalenes is not simple from the theoretical standpoint. 1-Halo-2-nitronaphthalenes react 10–20 times as fast as the 2-halo-1-nitro isomers with piperidine (25°) or hydroxide ion (75°). This relation, which in general results from differences in E_A , is only partly due to decreased activation by the 1-nitro group as a result of interference with coplanarity (in the activating NO_2 resonance) by the *peri* hydrogen substituent.^{600a} Steric hindrance by the *peri*-CH group to nucleophilic substitution was considered as a possible explanation of the equal reactivity of 1- and 2-halonaphthalenes and tested experimentally.^{487, 642} 1-Chloroisoquinoline (*peri*-CH) does not have a higher E_A and lower k than 2-chloroquinoline (Tables X and XIV). Molecular models of the *non-planar* intermediate complex indicate that the hindrance is not appreciable. The 3-fold difference between the rates of piperidino-debromination of 8- and 6-bromo-1-nitronaphthalenes cannot be ascribed to α - vs. β -reactivity. The 8-halo compound is more activated inductively from the adjoining ring (the distance between substituents being about one-half that in the isomer), and its reaction seems certain to be accelerated by hydrogen bonding (cf. structure 13) in the transition state.^{73, 97c, 97e, 97f, 403}

The activation of all the positions in *quinoline* in relation to each other and to those in naphthalene can be judged from the kinetic study of piperidino-debromination^{611, 617, 642} (Tables IX and X) summarized in the following tabulation (res. = resonance activation, ind. = inductive activation).

	Naphthalene		Quinoline						
	1-Br	2-Br	2-Br	3-Br	4-Br	5-Br	6-Br	7-Br	8-Br
Relative rate (200°)	1	2	ca. 10^6	9	high	2	5	17	27
Decrease in E_A	0	0	11	3	10	3	1	3	2
Activation	—	—	res.	ind.	res.	res.	ind.	res.	ind.

TABLE X
HALOQUINOLINES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTIONS

Line No.	Quinoline substituents	Nucleophile (solvent)	Rate constant ^a (temp. °C) 10 ⁶ <i>k</i> liter mole ⁻¹ sec ⁻¹	Activation energy ^b kcal mole ⁻¹	Entropy of activation ^c cal mole ⁻¹ deg ⁻¹	Ref.
1	2-Cl	piperidine (solvent ^d)	[(50°) 35.3] ^e	13.8	-43.2	184b, 486a, 637
2	2-Cl	piperidine (petr. ether)	(130°) 53.1	14.9	-44.0	617, 637
3	2-Cl	piperidine (toluene)	(90.4°) 19.5	12.9	-45.2	184b, 617
4	2-Cl	piperidine (EtOH) ^f	(20°) 0.15	15.6 ^g	-38.9[4.8 ^h]	55, 139, 184b
5	2-Cl	EtO ⁻ (EtOH) ^f	(20°) 0.63	23.1 ^g	-10.7[11.0 ^h]	55, 139
6	2-Cl	MeO ⁻ (MeOH)	(59.8°) 5.9	—	—	637, 139
	2-Cl	MeO ⁻ (MeOH)	(86.5°) 6.8 × 10 ²	24.2	-7.0	643b
7	2-Cl	<i>i</i> -PrO ⁻ (<i>i</i> -PrOH)	(77.6°) 28	—	—	637
8	2-Cl	<i>p</i> -TolSH (toluene)	(84.3°) 35.4	18.5	[6.9 ^h]	640
	2-Cl	<i>p</i> -TolSH (MeOH)	(86.5°) 1.68 × 10 ²	—	—	643c
	2-Cl-6-NO ₂	MeO ⁻ (MeOH)	(86.5°) <i>ca.</i> 6 × 10 ⁵	15.0	-21.0	655b
	2-Cl-4-CF ₃	MeO ⁻ (MeOH)	(86.5°) <i>ca.</i> 5 × 10 ⁴	17.2	-18.3	655b
	2-Cl-4-CH ₃ CO	MeO ⁻ (MeOH)	(86.5°) <i>ca.</i> 2 × 10 ⁴	20.2	-13.4	655b
9	2,4-Cl ₂	MeO ⁻ (MeOH)	(75°) ⁱ 1.14 × 10 ⁴	—	—	643b, 647
	2,4-Cl ₂ (2-position)	MeO ⁻ (MeOH)	(75°) 0.39 × 10 ⁴	19.6	-15.6	643b, 647
	2,4-Cl ₂ (4-position)	MeO ⁻ (MeOH)	(75°) 0.75 × 10 ⁴	20.0	-13.0	643b, 647

10	2-Cl-4-OCH ₃	MeO ⁻ (MeOH)	(75°) 40.6 (48.6)			647 (643b)
	2-Cl-4-OCH ₃	MeO ⁻ (MeOH)	(86.5°) 1.27 × 10 ²	20.0	- 23.1	647
11	2-Br	piperidine (solvent ^d)	[(50°) 2.7 × 10 ²] ^e	13.8 (12.8)	- 39.1	139, 486a, (641)
12	2-Br	piperidine (solvent ^d)	[(43.2°) 33] ^e	—	—	637
13	2-Br	MeO ⁻ (MeOH)	(49.7°) 3.66	—	—	637
14	2-Br	<i>i</i> -PrO ⁻ (<i>i</i> -PrOH)	(50.6°) 24.6	—	—	637
15	3-Br	piperidine (solvent ^d)	[(201°) 13.8] ^e	21.6	- 43.6	617
16	5-Br	piperidine (solvent ^d)	[(197.5°) 3.39] ^e	22.0	- 44.6	617
17	6-Br	piperidine (solvent ^d)	[(201.6°) 8.9] ^e	23.9 (24.4)	- 39.1	617 (641)
18	6-Br	piperidine (H ₂ O)	[(184°, 272 atm. ^f) 8.7] ^e	—	—	637
19	7-Br	piperidine (solvent ^d)	[(203.5°) 33.8] ^e	21.6	- 41.5	617
20	8-Br	piperidine (solvent ^d)	[(200°) 53.1] ^e	23.3 (21.0)	- 37.2	617 (641)
21	8-Br	piperidine (H ₂ O)	[(163°, 273 atm. ^f) 3.1] ^e	—	—	637

^a Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperatures given.

^b The Arrhenius activation energy,⁴⁷⁹ E_A .

^c Entropy of activation,⁴⁸² ΔS^\ddagger .

^d Carried out in the nucleophile as solvent.

^e Pseudo-unimolecular rate constant in sec⁻¹.

^f Water was added to absolute ethanol to make 99.8% ethanol.

^g Heats of activation,⁴⁸¹ ΔH^\ddagger , also given in article.

^h log₁₀ A; the Arrhenius frequency factor,⁴⁷⁹ A, is in liter mole⁻¹ sec⁻¹.

ⁱ The total rate constant for the reaction comprises a 1.9:1 ratio of 4- to 2-mono-substitution.

^j Atmospheres of pressure under which reaction was carried out.

TABLE XI

4-HALOQUINOLINES AND *N*-OXIDES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTIONS

Line No.	Quinoline substituents	Nucleophile (solvent)	Rate constant ^a (temp. °C) 10 ⁶ <i>k</i> liter mole ⁻¹ sec ⁻¹	Activation energy ^b kcal mole ⁻¹	Entropy of activation ^c cal mole ⁻¹ deg ⁻¹	Ref.
1	4-Cl	EtO ⁻ (EtOH ^d)	(20°) 0.65	20.4	-19.6 [9.0 ^e]	55, 139
2	4-Cl	MeO ⁻ (MeOH)	(86.5°) 6.3 × 10 ²	(23.6) 21.2	-17.2	643b (648), 649
	4-Cl	4-CH ₃ C ₆ H ₄ S ⁻ (MeOH)	(86.5°) 1.60 × 10 ³	—	—	643b
3	4-Cl	piperidine (solvent ^f)	[(100°) 17.1] ^g	16.1	-44.5	617
4	4-Cl	piperidine (solvent ^f)	[(80°) 6.0] ^g	14.9	[7.6 ^e]	365
5	4-Cl	piperidine (70% EtOH)	(100°) 39	20.6 ^h	-24	137, 184b
6	4-Cl-1-oxide	piperidine (70% EtOH)	(100°) 1.10 × 10 ³	10.8 ^h	-42	137
7	4-Cl-1-oxide	piperidine (95% EtOH)	(90°) 4.24 × 10 ²	8.0 ^h	-52	137
8	4-Cl-6-NO ₂	MeO ⁻ (MeOH)	(75.2°) 1.06 × 10 ⁵	17.0	-16.6	649
	4-Cl-7-NO ₂	MeO ⁻ (MeOH)	(75.2°) ca. 1 × 10 ⁴	19.4	-12.5	655b
9	2,4-Cl ₂ ⁱ	—	—	—	—	—
10	4,6-Cl ₂	MeO ⁻ (MeOH)	(86.5°) 4.25 × 10 ³	21.0	-13.2	649
11	4,6-Cl ₂	piperidine (solvent ^f)	[(80°) 31.6] ^g	15.4	[8.6 ^e]	365
12	4,7-Cl ₂	MeO ⁻ (MeOH)	(86.5°) 4.67 × 10 ³	18.1	-21.1	648, 649
13	4,7-Cl ₂	piperidine (solvent ^f)	[(80°) 47] ^g	13.8	[7.5 ^e]	365
14	4,8-Cl ₂	piperidine (solvent ^f)	[(80°) 56] ^g	12.6	[6.9 ^e]	365

15	4-Cl-2-OCH ₃	MeO ⁻ (MeOH)	(86.5°) 40	22.7	- 18.0	643b, 647
16	4-Cl-6-OCH ₃	MeO ⁻ (MeOH)	(86.5°) 1.48×10^2	22.9	- 14.7	649
17	4-Cl-7-OCH ₃	MeO ⁻ (MeOH)	(86.5°) 3.76×10^2	21.7	- 16.3	649
18	4-Cl-6-SCH ₃	MeO ⁻ (MeOH)	(86.5°) 9.5×10^2	22.2	- 13.2	649
	4-Cl-2-SCH ₃	MeO ⁻ (MeOH)	(86.5°) 3.2×10^2	18.7	- 22.1	643b
19	4-Cl-7-S-Tolyl	MeO ⁻ (MeOH)	(86.3°) 1.52×10^3	21.4	—	648
20	4-Cl-5-Me	piperidine (solvent) ^f	[(80°) 0.78] ^g	—	—	365
21	4-Cl-6-Me	piperidine (solvent) ^f	[(80°) 2.1] ^g	16.4	[8.0 ^e]	365
22	4-Cl-8-Me	piperidine (solvent) ^f	[(80°) 3.0] ^g	14.0	[6.7 ^e]	365
23	4-Br	piperidine (70% EtOH)	(100°) 75	17.0 ^h	- 32	137
24	4-Br	piperidine (95% EtOH)	(100°) 59	14.5 ^h	- 39	137
25	4-Br	piperidine (benzene)	(120°) 4.9	—	—	137
26	4-Br-1-oxide	piperidine (70% EtOH)	(100°) 1.56×10^3	12.4 ^h	- 36	137
27	4-Br-1-oxide	piperidine (95% EtOH)	(100°) 8.9×10^2	10.7 ^h	- 44	137
28	4-Br-1-oxide	piperidine (benzene)	(120°) 73	10.7 ^h	- 51	137
29	4-I	piperidine (70% EtOH)	(100°) 37	16.6 ^h	- 35	137
30	4-I-1-oxide	piperidine (70% EtOH)	(100°) 3.51×10^2	10.6 ^h	- 46	137

^a Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperatures given.

^b The Arrhenius activation energy, ⁴⁷⁹ E_A.

^c Entropy of activation, ⁴⁸² ΔS[‡].

^d Water was added to absolute ethanol to make 99.8% ethanol.

^e log₁₀ A; the Arrhenius frequency factor, ⁴⁷⁹ A, is in liter mole⁻¹ sec⁻¹.

^f Carried out in the nucleophile as solvent.

^g Pseudo-unimolecular rate constant in sec⁻¹.

^h Heats of activation, ⁴⁸¹ ΔH[‡], which differ from E_A by RT, about 0.6 kcal mole⁻¹ at 20°.

ⁱ See Table X.

The rate differences result primarily from the lowering of the activation energies, but in a few cases small entropy increases also contribute. The relatively high rate of reaction of 8-bromoquinoline (346) is postulated to be due to hydrogen bonding of the solvent, piperidine, to the nearby azine-nitrogen in the ground state and intramolecular hydrogen bonding of $\text{>N}^+-\text{H}$ to the ring-nitrogen in the transition state with a consequent accelerative increase in the entropy of activation relative to that of its isomers. The assembled data negate the statement⁶⁴⁶ that the reactivity of the α -positions in naphthalene is reflected in the reactivity of the 5- and 8-positions (345 and 346) in quinoline toward nucleophilic reagents. Resonance activation (at 2- and 4-positions in 353 and 348) is greater than inductive activation (at 3-position in 351) in the nitrogen-containing ring in terms of the rate and the decrease in E_A . The difference in the adjoining ring is small with the inductively activated 6-derivative (342) having the highest value for E_A . The 10-fold difference in rates for the 7- and 5-derivatives is considered to be due to greater stabilization by the *para,ortho*-quinoid transition state (341) for the 7-derivatives than by the *ortho,ortho*-quinoid structure (345) for the 5-compounds. However, one would expect this benefit to be reflected in the energy of activation, whereas an increased entropy of activation is partly responsible. It is apparent that inductive activation in the same ring as the azine-nitrogen is about as effective as resonance-activation from the adjoining ring. The lower rate of reaction of the resonance-activated 5-compound than of the inductively activated 6-isomer is an anomaly which occurs also in the nitro analogs discussed below and thus seems to be a general characteristic (cf. Section IV, A, 1) of the bicyclic system worth further study.

Activation by a para ring-nitrogen is generally greater than that by an *ortho* ring-nitrogen in quinolines, although the relationship of rates and of E_A varies. With alcoholic methoxide and ethoxide the rates (86° and 20°, respectively) of reaction of 4- and 2-chloroquinoline (348 and 353) are about equal⁶⁴⁷ (Table X, lines 5 and 6; Table XI, lines 1 and 2), but E_A for reaction at the 4-position is substantially lower. The 4-position is ten times as reactive toward methanolic tolylmercaptide at 86° (Table X, line 8; Table XI, line 2). In alcoholic solution, hydrogen bonding of the solvent to the azine-nitrogen can sterically decelerate reaction at the 2-position. This factor is considered as contributing to the change in the relative reactivity with the reaction medium: alcoholic piperidine vs. liquid piperidine. With piperidine in ethanol,

the rates (100°) at the 2- and 4-positions are equal (Table X, line 4; Table XI, line 5), while in piperidine as solvent (Table X, line 1; Table XI, line 3) the 2-halo compound has a lower E_A and a 60-fold greater rate (100°). In the latter reaction, hydrogen bonding of the reagent to the azine-nitrogen in the ground state reinforces the factors in the zwitterionic transition state (less separation of opposite charges and hydrogen bonding of $\text{>N}^+-\text{H}$ to the partly anionic ring-nitrogen) which favor reaction at the 2-position. In alcohol, hydrogen bonding of the solvent to the azine-nitrogen predominates.

Comparison of the *activation by an azine-nitrogen in ortho and para positions* can also be done in another way. The activation energy for ethoxylation (Table XI, line 1) of *para*-activated 4-chloroquinoline (348) is 2 kcal lower than that for *ortho*-activated 1-chloroisoquinoline (349) (Table XIV, line 3). The rates are equal (only at 20°) due to a large, compensating difference between the entropies of activation. In piperidino-dechlorination, 4-chloroquinoline (Table XI, line 3) has a higher E_A and a lower rate (by about 200-fold at 20°) than 1-chloroisoquinoline (Table XIV, line 1). This reversal of reactivity and of the relationship of the activation energies is attributed to the factors in *amination* reactions mentioned above. The relative reactivity of the chloro groups in 2,4-dichloroquinoline with methanolic methoxide is given⁶⁴⁷ as a 2:1 rate ratio of 4- to 2-displacement.

As summarized in the following tabulation, the relative rates of piperidino-debromination⁵⁹⁸ of the *halo-1-nitronaphthalenes* (data from Table XII, numbered to show relation to quinolines) provide a good confirmation of the relation of induction (ind.) to resonance activation (res.) and of the extent of transmission of activation to an adjoining ring. Here again, as in the quinoline series, the 8-isomer (346) is more reactive than its resonance-activated 5-bromo isomer (345) and its inductively activated 3- and 6-bromo isomers (351 and

1-Nitronaphthalene						
	3-Br	4-Br	5-Br	6-Br	7-Br	8-Br
Relative rate (107°)	7	ca. 10 ⁴	1	4	70	12
Activation	ind.	res.	res.	ind.	res.	ind.
Rate/Br-naphthalene ^a	100		25	50	1,000	300

^a Rate relative to those of 1- or 2-bromonaphthalene, as appropriate.

TABLE XII
HALO-1-NITRONAPHTHALENES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTIONS

Line No.	1-Nitronaphthalene substituents	Nucleophile (solvent)	Rate constant ^a (temp. °C) 10 ⁶ k liter mole ⁻¹ sec ⁻¹	Activation energy ^b kcal mole ⁻¹	Frequency factor ^c log ₁₀ A	Ref.
1	2-Cl	HO ⁻ (aq. organic ^d)	(75°) 7.4 ^b	17.5	—	650, 651
2	2-Cl	EtO ⁻ (EtOH ^e)	(65°) 77	—	—	651
3	2-Cl	piperidine (solvent ^f)	[(25°) 1.3 × 10 ²] ^g	11.6	8.2	612
4	2-Br	piperidine (solvent ^f)	[(25°) 1.7 × 10 ²] ^g	12.3	8.8	612
5	2-Br	piperidine (C ₆ H ₆)	[(80°) 1.4 × 10 ³] ^g	—	—	598
6	2-I	piperidine (solvent ^f)	[(0°) 2.1] ^g	—	—	612
	2-I	piperidine (solvent ^f)	[(25°) 21] ^g	14.8	9.7	612
7	3-Br	piperidine (solvent ^f)	[(107°) 0.72] ^g	—	—	598
8	4-Cl	HO ⁻ (aq. organic ^d)	(75°) 30.3 ^h	14.8	—	650, 651
9	4-Cl	MeO ⁻ (MeOH)	(60°) 3.78 × 10 ²	19.9	9.6	652
10	4-Cl	MeO ⁻ (MeOH)	(60°) 3.80 × 10 ²	23.3	[-6.5] ⁱ	600a
11	4-Cl	EtO ⁻ (EtOH)	(60°) 3.83 × 10 ²	—	—	651, 652

12	4-Cl	piperidine (95% EtOH)	(90°) 2.64×10^2	11.4	—	137
13	4-Cl	piperidine (EtOH)	(60°) 43.6	12.1	3.6'	654
14	4-Cl	piperidine (C ₆ H ₆)	(60°) 0.4	14.9	3.4'	652
15	4-Br	piperidine (95% EtOH)	(90°) 3.54×10^2	—	—	137
16	4-Br	piperidine (C ₆ H ₆)	(60°) 1.61	15.0	4.1'	652
17	4-Br	piperidine (C ₆ H ₆)	[(80°) 170] ^g	—	—	598
18	5-Br	piperidine (solvent ^f)	[(107°) 0.11] ^g	—	—	598
19	6-Br	piperidine (solvent ^f)	[(107°) 0.42] ^g	—	—	598
20	7-Br	piperidine (solvent ^f)	[(107°) 7.0] ^g	—	—	598
21	8-Br	piperidine (solvent ^f)	[(107°) 1.2] ^g	—	—	598

^a Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperatures given.

^b The Arrhenius activation energy,⁴⁷⁹ E_A .

^c The Arrhenius frequency factor,⁴⁷⁹ A , is in liter mole⁻¹ sec⁻¹.

^d Water-dioxane in 40:60 volume ratio.

^e At least 95% of the reaction was ethoxylation using KOH in 99.6% ethanol.

^f Carried out in the nucleophile as solvent.

^g Pseudo-unimolecular rate constant in sec⁻¹.

^h Later paper gave rates only one-half this value.

ⁱ Entropy of activation in cal mole⁻¹ deg⁻¹.

^j Entropy of activation,⁴⁸² ΔS^\ddagger , in cal mole⁻¹ deg⁻¹ for line 12 is -44, for line 13 is -44.5, for line 14 is -45.8, and line 16 is -42.5.

342). Hydrogen bonding of $\text{>N}^+\text{—H}$ to the oxygen atom of a nitro group in the transition state appears to be the most reasonable explanation. The greater reactivity of the 7-bromo derivative (341) compared to the 5-bromo compound (345) can be attributed to the lower energy of the *para,ortho*-quinoid transition state (341) for the former than of the *ortho,ortho*-quinoid structure (345) for the 5-isomer. The anomalous relation of the 5- and 6-derivatives is discussed above with the quinoline analogs. In semi-quantitative comparisons of amino-dechlorination⁶⁰² or piperidino-debromination^{600b, 602} of 2-, 4-, 5-, and 8-halo-1-nitronaphthalenes and of hydroxide displacements⁶⁰³ of the azido group in 2-, 4-, 5-, and 7-azido-1-nitronaphthalenes, it was demonstrated that activation from the adjoining ring occurs but is much less effective than from a position in the same ring as the leaving group. Resonance activation in the 5-halo and 5-azido compounds was poor.^{600b, 602, 603}

The reactivities of 4- and 2-halo-1-nitronaphthalenes can usefully be compared with the behavior of azine analogs to aid in delineating any specific effects of the naphthalene π -electron system on nucleophilic substitution. With hydroxide ion (75°) as nucleophile (Table XII, lines 1 and 8), the 4-chloro compound reacts four times as fast^{650, 651} as the 2-isomer, which has the higher E_A , and, with ethoxide ion (65°) (Table XII, lines 2 and 11), it reacts about 10 times as fast.⁶⁵¹ With piperidine (Table XII, lines 5 and 17) the reactivity relation at 80° is reversed, the 2-bromo derivative reacts about 10 times as rapidly as the 4-isomer, presumably due to hydrogen bonding or to electrostatic attraction in the transition state, as postulated for benzene derivatives.^{73, 97c, 97e, 97f, 403} 4-Chloro-1-nitronaphthalene reacts 6 times as fast with methanolic methoxide (60°) as does 4-chloroquinoline due to a considerably higher entropy of activation and in spite of a higher E_A (by 2 kcal).^{600a}

The halo-2-nitronaphthalenes (Table XIII) enable one to draw tentative conclusions about *intranuclear* and *internuclear* activation in the isoquinolines for which data are not available. These compounds are numbered so as to show their relation to their isoquinoline analogs. The relative rates are summarized in the following tabulation along with the ratio of the rates of piperidino-debromination to that of the appropriate bromonaphthalene (res. = resonance activation, ind. = inductive activation).

TABLE XIII
HALO-2-NITRONAPHTHALENES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTIONS

Line No.	2-Nitronaphthalene substituents	Nucleophile (solvent)	Unimolecular rate constant ^a (temp. °C) $10^6 k$, sec ⁻¹	Activation energy ^b kcal mole ⁻¹	Frequency factor ^c log ₁₀ A	Ref.
1	1-Cl	HO ⁻ (aq. organic ^d)	[(75°) 1.56×10^2] ^{e,f}	21.8	—	650, 651
2	1-Cl	piperidine (solvent ^g)	(25°) 1.28×10^3	10.9	8.7	612
3	1-Cl	piperidine (EtOH)	[(60°) 2.01×10^2] ^e	15.6	6.6 ^h	654
4	1-Br	piperidine (solvent ^g)	(25°) 1.53×10^3	10.4	8.4	612
5	1-Br	piperidine (C ₆ H ₆)	(80°) 5.6×10^3	—	—	598
6	1-I	piperidine (solvent ^g)	(25°) 2.38×10^2	13.5	9.8	612
7	3-Br	piperidine (C ₆ H ₆)	(80°) 7.0	—	—	598
8	3-Br	piperidine (solvent ^g)	(107°) 97	—	—	598
9	4-Br	piperidine (solvent ^g)	(107°) 1.1	—	—	598
10	6-Br	piperidine (solvent ^g)	(107°) 7.0	—	—	598
11	7-Br	piperidine (solvent ^g)	(107°) 0.42	—	—	598

^a Pseudo-unimolecular rate constants.

^b The Arrhenius activation energy,⁴⁷⁹ E_A.

^c The Arrhenius frequency factor,⁴⁷⁹ A, is in liter mole⁻¹ sec⁻¹.

^d Water-dioxane in 40:60 volume ratio.

^e Bimolecular rate constant in liter mole⁻¹ sec⁻¹.

^f Later paper gave rates only one-half this value.

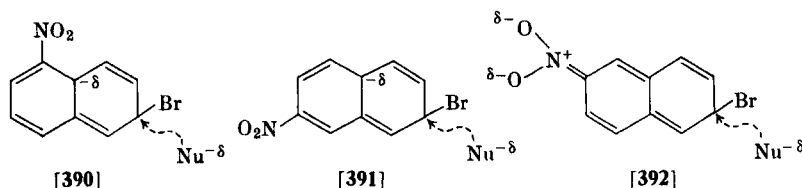
^g Carried out in the nucleophile as solvent.

^h Entropy of activation,⁴⁸² ΔS[‡], is -30.8 cal mole⁻¹ deg⁻¹.

	2-Nitronaphthalene				
	1-Br	3-Br	4-Br	6-Br	7-Br
Relative rate (107°)	ca. 10 ⁶	250	2.5	17	1
Activation	res.	res.	ind.	res.	ind.
Rates/Br-naphthalene ^a	ca. 10 ⁸	13,000	250	1,000	50

^a Rate relative to those of 1- or 2-bromonaphthalene, as appropriate.

It is noteworthy that the inductive effect in the quinolines and in these two groups of nitro compounds is 1.7–2.7 times greater in the azine ring than in the adjoining ring, which fits approximately the relative distance apart (via the σ -bonds or through space). The equal rates of reaction of compounds **390** and **391** in piperidino-debromination shows that the distance of the nitro group from the negative charge is not as significant as the distance through space from the site of attack. The inductive effect in the same ring is about



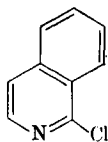
one-fourth as accelerative as resonance activation from the 6-position in the adjoining ring. The latter derivative has the favorable “*amphi*” or *para,para*-quinoid resonance structure **392** which is still qualitatively⁶⁰² and quantitatively much less effective than resonance stabilization in the same ring (1-Br or 3-Br derivatives). Inductive activation in the “equidistant” 4-bromo-2-nitro- and 3-bromo-1-nitro-naphthalenes leads to rates which are nearly the same. Piperidino-debromination of the 1- and 3-derivatives of 2-nitronaphthalene is expected to be accelerated, relative to that of the isomers, by “built-in solvation” characteristic of amination of *ortho*-nitro derivatives^{73, 97c, 97e, 97f, 403} but not of alkoxylation, etc.

The reactivities of the 1-bromo- and 3-bromo-2-nitronaphthalenes (Table XIII, lines 4, 5, 7 and 8) are markedly different as are those of the isoquinoline analogs discussed below. The uniquely unfavorable

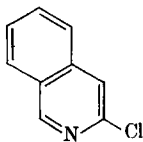
character of the 2,3-orientation in the bicyclic system is evident from the low reaction rate produced by this particular resonance activation and from the fact that the 3-bromo compound reacts with piperidine much less readily⁶⁰² than does 2-bromonitrobenzene. The rate of piperidino-debromination (80°) of the 3-bromo compound is less than that of the 4-bromo-1-nitro isomer (Table XII, line 16) which lacks the benefit of "built-in solvation." However, this resonance activation is not inappreciable as is sometimes stated.^{55, 618} Activation in the 2,3-orientation cannot be considered as merely inductive since it increases the reaction rate 100 times as much as does the inductive effect in 4-bromo-2-nitronaphthalene and in 3-bromo-1-nitronaphthalene. Its acceleration is greater by about 15-fold than that of resonance activation from the 6-position in the adjoining ring.

There are ten possible ways to fuse a benzene ring onto the monocyclic azines. Seven of these are "normal" in the sense of leading to bicyclic compounds whose reactivity is increased due to enlarging the resonating system in which the charge is stabilized. Three of these fusions are "abnormal" in that they produce bicyclic compounds of relatively low reactivity; the reactivity may even be decreased relative to that of the monocyclic analog. Inductive activation in an azine is not appreciably affected by benzo-fusion since this activation through space or along the chain of atoms depends primarily on the distance between the leaving group and the activating center, according to the pertinent data tabulated in this section.

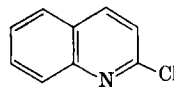
The monoazaphthalenes provide a good illustration of the effect of benzo-fusion onto an azine and of the variation of the effect with the position of fusion. A benzo ring can be fused onto 2-chloropyridine at the 3,4- [leading to 1-chloroisoquinoline (393)], at the 4,5- [forming 3-chloroisoquinoline (394)], or at the 5,6-position [yielding 2-chloroquinoline (395)]. The first and the last fusions



[393]



[394]



[395]

lead to bicyclic compounds whose activation energies and rates of reaction (20°) with piperidine (Table XIV, lines 1 and 2; Table X,

TABLE XIV
CHLOROISOQUINOLINES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTIONS

Line No.	Isoquinoline substituents	Nucleophile (solvent)	Rate constant ^a (temp. °C) 10 ⁶ <i>k</i> liter mole ⁻¹ sec ⁻¹	Activation energy ^b kcal mole ⁻¹	Entropy of activation ^c cal mole ⁻¹ deg ⁻¹	Frequency factor ^d log ₁₀ A	Ref.
1	1-Cl	piperidine (solvent ^e)	[(20.8°) 2.7] ^f	13.5	-44.7	—	487
2	1-Cl	piperidine (EtOH ^g)	(20°) 0.25	14.5 ^h	-41.9	4.2	55, 139
3	1-Cl	EtO ⁻ (EtOH ^g)	(20°) 0.69	22.5 ^h	-12.3	10.7	55, 139
4	3-Cl	EtO ⁻ (EtOH ^g)	(20°) 1.2 × 10 ⁻⁵	32.4 ^h	-0.7	13.2	55, 139
5	3-Cl	piperidine (EtOH ^g)	(145°) 1.11 × 10 ⁻²	—	—	—	55

^a Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperatures given.

^b The Arrhenius activation energy,⁴⁷⁹ E_A.

^c Entropy of activation,⁴⁸² ΔS[‡].

^d The Arrhenius frequency factor,⁴⁷⁹ A, is in liter mole⁻¹ sec⁻¹.

^e Carried out in the nucleophile as solvent.

^f Pseudo-unimolecular rate constant in sec⁻¹.

^g Water was added to absolute ethanol to make 99.8% ethanol.

^h Heats of activation,⁴⁸¹ ΔH[‡], also given in article.

lines 1 and 4) and with ethoxide ion (Table XIV, line 3; Table X, line 5) are essentially the same; however, the 4,5-fusion leads to a structure which reacts 10^5 times more slowly with these reagents. In contrast to the other benzo-fusions, the latter (394) *deactivates* the chloro-azine: with ethoxide ion (20°), the rate is decreased by 180-fold and E_A is 5.6 kcal higher with respect to 2-chloropyridine; with piperidine, the rate (20°) is lower than that of the monocycle by 400-fold. On the other hand, ethoxylation (20°) of 2-chloroquinoline and of 1-chloroisoquinoline proceeds faster by 3,000-fold, due to lower E_A (ca. 4 kcal less), than that of 2-chloropyridine (Table II, p. 270). The rates of piperidino-dechlorination (20°) of these bicyclic compounds are 300–600-fold greater than that of 2-chloropyridine due to a 4–5 kcal lowering of E_A . The effect of benzo-fusion onto the more reactive 4-chloropyridine (Table II, p. 270) increases the rate of ethoxylation (20°) by only 8-fold. Additional benzo-fusion to the heterocyclic ring of quinolines or of isoquinolines to yield acridines or phenanthridines increases the reactivity^{55,615} toward nucleophilic substitution, but fusion to their carbocyclic rings produces a negligible effect.⁶⁵³ Ethoxylation (20°) of 9-chloroacridine (*Chemical Abstracts'* numbering) proceeds about 100 times as fast as that of 4-chloroquinoline (ΔS^\ddagger same for both, E_A 2.7 kcal lower for the former).⁵⁵

As already mentioned, there is a striking difference in the reactivity of 1- and 3-chloroisoquinoline; the former reacts about 10^5 times faster than the latter with both piperidine and ethoxide ion at room temperature. The lower rate of ethoxy-dechlorination of the 3-isomer is due to an E_A which is 10 kcal higher. It is not justified to conclude that this isomer is "virtually unactivated"⁵⁵ when its rate of ethoxylation is 100,000 times that of 2-chloronaphthalene and the E_A for this reaction is markedly decreased (by 7 kcal) relative to that of 2-chloronaphthalene. A direct comparison of reactivity with piperidine has not been made, but a rate ratio of 500:1 can be estimated by using a factor of one-fortieth (Table X, lines 1 and 4) to make the 2-chloronaphthalene data (Table IX, line 8) comparable to those for 3-chloroisoquinoline (Table XIV, line 5). Thus, activation at the 3-position of isoquinoline cannot be disregarded.⁶¹⁸

Benzo-fusion onto halonitrobenzenes (Table VIII, p. 277) produces acceleration^{652,654} of aminations or alkoxylation (Tables XII and XIII) except for 3-halo-2-nitronaphthalenes which are analogous to 3-haloisoquinolines.

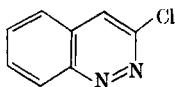
The composite results of *benzo-fusion* on the rates and activation energies of ethoxylation and of piperidination are summarized in round numbers in Scheme VI to give a broad perspective.

SCHEME VI

Benzo-fusion analogs		Effect of benzo-fusion	
		On the rate	On E _A
2-Cl-pyridine	1-Cl-isoquinoline	300-2000-fold increase	- 5 kcal
2-Cl-pyridine	3-Cl-isoquinoline	200-400-fold decrease	+ 6 kcal
2-Cl-pyridine	2-Cl-quinoline	300-3000-fold increase	- 4 kcal
4-Cl-pyridine	4-Cl-quinoline	10-fold increase	- 1 kcal
3-Cl-pyridazine	1-Cl-phthalazine	— ^a	— ^a
3-Cl-pyridazine	3-Cl-cinnoline	—	—
4-Cl-pyridazine	4-Cl-cinnoline	— ^a	— ^a
2-Cl-pyrimidine	2-Cl-quinazoline	up to 2-fold increase	- 1 to 0 kcal
4-Cl-pyrimidine	4-Cl-quinazoline	1000-fold increase	- 4 kcal
2-Cl-pyrazine	2-Cl-quinoxaline	10-fold increase	- 2 kcal

^a Data available only on the bicyclic azine.

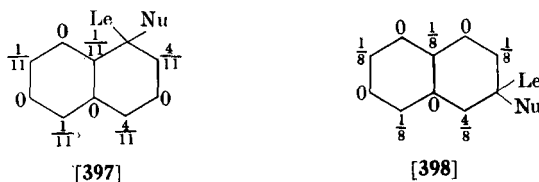
Even though data for a quantitative comparison are lacking, the effect of the position of benzo-fusion onto pyridazines is analogous to that with pyridines in producing the very poorly reactive 3-chloro-cinnoline (**396**) and highly reactive 1-chlorophthalazine (Table XV, lines 8 and 9).



[396]

Fusion onto 4-chloropyrimidine (Table III, p. 272) gives substantial activation for ethoxylation or piperidination, while benzo-fusion onto 2-chloropyrimidine (Table III) produces little change in the reactivity. In 2-chloroquinazoline (**400**) so formed, as in 3-chloro-cinnoline (**396**) and -isoquinoline (**399**), the benefit of resonance stabilization of charge on the ring-nitrogen is partly lost due to the high energy of the associated *ortho,ortho*-quinoid resonance structure. Another way of showing this bicyclic limitation on resonance activation is to compare the effects of insertion of another ring-nitrogen into

4-chloro- and 2-chloro-quinolines (**406** and **401**). The hypothetical conversion of the former into 4-chloroquinazoline (**405**) (Table XV, line 4) lowers E_A for piperidination by an estimated 11 kcal and produces an estimated 10^7 -fold increase in the rate, while conversion of the latter into 2-chloroquinazoline (**400**) (Table XV, line 3) lowers E_A by 4.5 kcal and increases the rate by about 10^3 -fold. This difference



of 10^4 in the rate can be rationalized by means of the negative charge densities in the naphthalene intermediate complexes **397** and **398** calculated by the Longuet-Higgins method.⁵⁵ In the 4-Le bicyclic complex **397**, a ring-nitrogen placed at the 3-position should have an effect comparable to one inserted at the 1-position since it stabilizes an equal fraction of the charge. However, in the 2-Le analog **398**, the fraction of the charge which can be stabilized by a nitrogen atom at the 3-position is much less. The relative energies of the charge-stabilizing resonating systems in the bicyclic transition states are responsible for the reactivities rather than "poor transmission"^{55, 618-621} of activation to the adjacent position by the "single" bond in the ground state (cf. Section IV, A, 1).

Benzo-fusion to 2-chloropyrazine (Table IV, p. 273) to form 2-chloroquinoxaline (**402**) produces a 12-fold acceleration of piperidination^{55, 487} (88°) with a concomitant decrease of about 2 kcal in E_A . The rate of piperidination (20°) of 2-chloroquinazoline (**400**) is only about 8 times that of 2-chloroquinoxaline (Table XV, line 7) and the rate of ethoxylation (20°) is only about one-third that of the quinoxaline. The rate relation in the former reaction is largely an entropy of activation difference, possibly resulting from greater hydrogen bonding of the reagent to the quinazoline derivative. The similarity of the rates of the two compounds in both reactions is unusual in equating resonance activation with inductive activation. The latter is unaffected by the bicyclic system, while resonance stabilization of charge in the 2,3-orientation is poor in bicyclics.

From the qualitative indications of preparative organic chemistry, it is clear that additional ring-nitrogens in bicyclic azines increase

TABLE XV
HALODIAZANAPHTHALENES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTIONS

Line No.	Substrates	Nucleophile (solvent)	Rate constant ^a (temp. °C) 10 ⁶ <i>k</i> liter mole ⁻¹ sec ⁻¹	Activation energy ^b kcal mole ⁻¹	Entropy of activation ^c cal mole ⁻¹ deg ⁻¹	Frequency factor ^d log ₁₀ A	Ref.
1	4-Cl-cinnoline	EtO ⁻ (EtOH [*])	(20°) 4.77 × 10 ³	15.8 ^f	-17.3	9.5	55, 139
2	2-Cl-quinazoline	EtO ⁻ (EtOH [*])	(20°) 2.98 × 10 ³	16.8 ^f	-15.9	9.9	55, 139
3	2-Cl-quinazoline	piperidine (EtOH [*])	(20°) 4.79 × 10 ²	11.1 ^f	-37.8	—	55
4	4-Cl-quinazoline	piperidine (EtOH [*])	(20°) ^g 3.1 × 10 ⁶	7.0 ^f	-37.5	5.1	55, 139 487
5	2-Cl-quinoxaline	EtO ⁻ (EtOH [*])	(20°) 8.28 × 10 ³	15.4 ^f	-18.2	—	55
6	2-Cl-quinoxaline	piperidine (toluene)	(88°) 2.37 × 10 ²	11.4	-46.2	—	487
7	2-Cl-quinoxaline	piperidine (EtOH [*])	(20°) 63.6	11.3 ^f	-40.9	—	55
8	1-Cl-phthalazine	EtO ⁻ (EtOH [*])	(20°) 1.86 × 10 ³	16.5 ^f	-16.9	9.5	55, 139
9	1-Cl-phthalazine	piperidine (EtOH [*])	(20°) 20	11.8 ^f	-42.0	4.2	55, 139

^a Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperatures given.

^b The Arrhenius activation energy,⁴⁷⁹ E_A .

^c Entropy of activation,⁴⁸² ΔS^\ddagger .

^d The Arrhenius frequency factor,⁴⁷⁹ A, is in liter mole⁻¹ sec⁻¹.

^e Water was added to absolute ethanol to make 99.8% ethanol.

^f Heats of activation,⁴⁸¹ ΔH^\ddagger , also given in ref. 55.

^g Rate measured at 0° was 0.275 liter mole⁻¹ sec⁻¹.

their reactivity toward nucleophiles. The effect often seems to be greater, but actually is not, when the azine-nitrogen is inserted into a ring already containing a ring-nitrogen and high reactivity at low temperature thereby is produced.

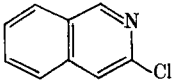
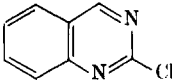
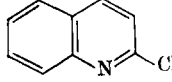
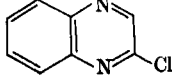
Three comparisons of *para* vs. *ortho* activation by an *additional ring-nitrogen* are possible from the available data and all show the former to be more effective, as found for the nitronaphthalenes above and for monocyclic azines (Section III). In piperidino-dechlorination of chloroquinazolines (Table XV, lines 3 and 4), the 4-isomer (**405**) reacts 6,500-fold faster than the 2-chloro compound (**400**) due entirely to a 4.1 kcal decrease in E_A , the ΔS^\ddagger being the same for both. However, this comparison is complicated by other differences (principally the "2-Le-3-aza effect"). The situation (Table XV, lines 1 and 8) is clear-cut for 4-chlorocinnoline (**407**) compared to 1-chlorophthalazine (**403**) in ethoxylation. The energy of activation for ethoxylation of 4-chloroquinoline (**406**) is lower by 2.2 kcal than for 1-chloroisoquinoline (**404**) while the reaction rates are the same (only at 20°) due to a compensating difference in ΔS^\ddagger .

The effect of insertion of an additional ring-nitrogen capable of resonance stabilization of the negative charge is evident from the relation of **400** to **399** and **401**. The quantitative effect is much greater in the less reactive **399**, for reasons already discussed. Activation by induction is evident from **402**, **403**, and **407** (cf. Schemes VII and VIII).

The insertion of a second ring-nitrogen *para* to the leaving group, 4-chloroquinazoline (**405**) vs. 1-chloroisoquinoline (**404**), increases the rate of piperidination by 10^7 -fold due to a 7.5 kcal decrease in E_A . In contrast, the insertion *ortho* to the leaving group, 2-chloroquinazoline (**400**) vs. 2-chloroquinoline (**401**), increases the rate by only 3,000-fold due to a proportionately smaller decrease of 4.5 kcal in E_A . The effect of the bicyclic system in this 2,3-relation is discussed above. The insertion of a second ring-nitrogen *meta* to the leaving group produces a substantial inductive activation by lowering the activation energy: **404** vs. **403** and **406** vs. **407**. The rates of piperidination and ethoxylation are increased approximately 100–10,000-fold.

The low reactivity (Section IV, B, 3, a) of 3-chlorocinnoline compared to that of its isomer **407** is the combined result of decreased activation by an *ortho* ring-nitrogen and of the effect of the bicyclic system on charge stabilization in 2,3-orientations. The "2-Le-3-aza effect" alone is the reason that the reactivity of 3-chlorocinnoline (**396**) is much lower than that of its benzopyridazine isomer **403**.

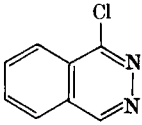
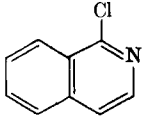
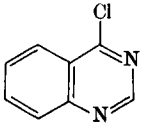
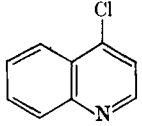
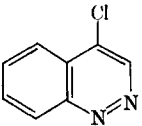
SCHEME VII. Activation by Additional Ring-Nitrogen.
2-Chloroazanaphthalenes

Structure	Piperidination		Ethoxylation	
	Relative rate (20°)	Change in E _A	Relative rate (20°)	Change in E _A
 [399]	10 ⁻⁵ (estimated)	—	10 ⁻⁵	+ 9.3
 [400]	3,200	- 4.5	20,000	- 6.3
 [401]	1	standard	4 ^a	standard
 [402]	400	- 4.3	50,000	- 7.7

^a Based on rate of piperidination, taken as unity.

There are no kinetic data on azanaphthalenes containing three or more ring-nitrogens. The halo-polynitronaphthalenes (Table XVI, numbered so as to correspond to azanaphthalenes) provide a few indications of the magnitude of activation to be expected in bicyclic polyazines. In a rough comparison of the time and temperature necessary for complete amination, van der Kam^{65a} found that insertion of a 6- or 8-nitro group into 1,8- or 1,6-dinitronaphthalenes produced an increase (estimated 50-fold) in the reactivity of 2-halo or 2-alkoxy groups. Reaction of 4-chloro- or 4-bromo-1-nitronaphthalenes with piperidine is accelerated 20-fold by insertion of an 8-nitro group.^{65b} Resonance activation by a third nitro group in the 8-position produces only a 5-fold acceleration of methoxylation^{63c}

SCHEME VIII. Activation by Additional Ring-Nitrogen.
4-Chloroazanaphthalenes

Structure	Piperidination		Ethoxylation	
	Relative rate (20°)	Change in E_A	Relative rate (20°)	Change in E_A
 [403]	160	-2.7	10 ⁴	-6.0
 [404]	2 ^a	standard	4 ^a	standard
 [405]	10 ⁷	-7.5	—	—
 [406]	—	—	4	-2.2
 [407]	—	—	10 ⁴	-6.7

^a Based on rate of piperidination of 401, taken as unity.

TABLE XVI
HALOPOLYINITRONAPHTHALENES. KINETIC DATA ON NUCLEOPHILIC SUBSTITUTIONS

Line No.	Naphthalene substituents	Nucleophile (solvent)	Rate constant ^a (temp. °C) 10 ⁶ <i>k</i> liter mole ⁻¹ sec ⁻¹	Activation energy ^b kcal mole ⁻¹	Entropy of activation ^c cal mole ⁻¹ deg ⁻¹	Frequency factor ^d log ₁₀ A	Ref.
1	4-Cl-1,3-(NO ₂) ₂	MeO ⁻ (MeOH)	(0°) 5.8 × 10 ⁴	11.5	—	7.9	638, 652
2	4-Cl-1,3-(NO ₂) ₂	EtO ⁻ (EtOH)	(0°) 1.62 × 10 ⁵	9.9	—	7.1	638, 652
3	4-Cl-1,3-(NO ₂) ₂	piperidine (EtOH)	(60°) 2.38 × 10 ⁶	4.4	-45.5	3.3	654
4	4-Cl-1,3-(NO ₂) ₂	piperidine (C ₆ H ₆)	(60°) 3.85 × 10 ⁶	5.9	-40.1	4.5	652
5	4-Br-1,3-(NO ₂) ₂	piperidine (C ₆ H ₆)	(60°) 6.14 × 10 ⁶	8.1	-32.5	6.1	652
6	4-Cl-1,8-(NO ₂) ₂	piperidine (C ₆ H ₆)	(60°) 7.71	11.4	-50.2	2.4	652
7	4-Br-1,8-(NO ₂) ₂	piperidine (C ₆ H ₆)	(60°) 28	11.6	-46.9	3.1	652
8	4-Cl-1,3,8-(NO ₂) ₃	MeO ⁻ (MeOH)	(0°) 3.3 × 10 ⁵	—	—	—	638
9	2-Cl-1,6,8-(NO ₂) ₃	MeO ⁻ (MeOH)	(0°) 3.7 × 10 ⁴	—	—	—	655a
10	2-Br-1,6,8-(NO ₂) ₃	MeO ⁻ (MeOH)	(0°) 2.0 × 10 ⁴	—	—	—	655a

^a Bimolecular rate constants determined at temperatures giving conveniently measurable rates and calculated for the temperatures given.

^b The Arrhenius activation energy,⁴⁷⁹ *E*_A.

^c Entropy of activation,⁴⁸² *ΔS*[‡].

^d The Arrhenius frequency factor,⁴⁷⁹ A, is in liter mole⁻¹ sec⁻¹.

of the 4-halo-polynitronaphthalenes (Table XVI, lines 1 and 8) due to the "4-Le-8-aza effect" (Section IV, A, 1). Comparison of resonance activation in the same ring (1,3-dinitro compounds, Table XVI, lines 4 and 5) with that from the adjoining ring (1,8-dinitro compounds, lines 6 and 7) reveals a 10^5 -fold lower rate for the latter, which again involve the "4-Le-8-aza effect." The major part of this rate difference arises from the decreases in E_A although increases in ΔS^\ddagger contribute to the total effect.

Some recent results of Illuminati *et al.*^{65b} demonstrate a 10-fold greater rate of methoxy-dechlorination of 4-chloroquinolines and 2-chloroquinoxalines by a 6-nitro than by a 7-nitro group; the former accelerates the reaction by about 1,000-fold. The 6-substituent produces the greater decrease in activation energy by lowering the electron-repulsion to attack by the nucleophile and by stabilizing the transition state as a result of resonance.

The rate of amination and of alkoxylation increases 1.5–3-fold for a 10° rise in the temperature of reaction for naphthalenes (Table X, lines 1, 2, 7 and 8), quinolines,⁵⁵ isoquinolines,⁵⁵ 1-halo-2-nitronaphthalenes,⁶¹² and diazanaphthalenes.⁵⁵ The relation of reactivity can vary or be reversed, depending on the temperature at which rates are mathematically or experimentally compared (cf. naphthalene discussion above and Section III, A, 1). For example, the rate ratio of piperidination⁵⁵ of 4-chloroquinazoline to that of 1-chloroisoquinoline varies 100-fold over a relatively small temperature range: 10^7 at 20° , and 10^5 at 100° . The ratio of rates of ethoxylation⁵⁵ of 2-chloropyridine and 3-chloroisoquinoline is 9 at 140° and 180 at 20° . Comparison of 2-chloro- with 4-chloro-quinoline gives a ratio of 2.1 at 90° and 0.97 at 20° ; the ratio for 4-chloro-quinoline and -cinnoline is 3200 at 60° and 7300 at 20° ; and piperidination⁵⁵ of 2-chloroquinoline vs. 1-chloroisoquinoline has a rate ratio of 1.0 at 110° and 1.7 at 20° . The change in the rate ratio with temperature⁴⁷⁹ will depend on the difference in the heats of activation of the two reactions (Section III, A, 1).

The effect of solvent on the rate, E_A , and ΔS^\ddagger can be derived from the data on haloquinolines and their *N*-oxides (Tables X and XI), on halonitronaphthalenes (Tables XII and XIII), and on halodinitronaphthalenes (Table XVI). Depending on the nature of the reaction, the relative reactivity of two compounds can be substantially different in different solvents. For example, piperidination of 2-chloroquinoline (Table X, lines 3 and 4) compared to 2-chloroquinoxaline (Table XV,

lines 6 and 7) has a rate ratio of 1:425 in ethanol (20°) and 1:12 in toluene (90°). The rate ratio for piperidination of 2,4-dinitro- vs. 4-nitro-1-chloronaphthalenes and of 2-nitro- vs. 4-nitro-1-chloronaphthalenes is much larger in benzene than in alcohol. For the latter, the ratio is 663:1 in benzene and about 5:1 in alcohol.⁶⁵⁴ In such aminations, this change in the ratio with solvent is an entropy effect.^{73, 97c}

The work of Okamoto *et al.*¹³⁷ on quinoline and quinoline-1-oxides (Table XI) provides the following relation of solvent to the rate of reaction with piperidine: $k_{70\% \text{ alc.}} = 1.5\text{--}2.5 \times k_{95\% \text{ alc.}} = 80\text{--}200 \times k_{\text{benzene}}$. The entropy and energy of activation increase with the polarity of these solvents.

The nucleophile has specific effects on the rate, the activation energy, and the entropy of activation. The activation energies for substitution with the anionic nucleophiles HO^- , EtO^- , and MeO^- are substantially *greater* than those with piperidine for naphthalenes (Table IX), nitronaphthalenes (Tables XII and XVI), quinolines (Tables X and XI), isoquinolines (Table XIV), and bicyclic diazines (Table XV). The rates with the anionic nucleophiles are greater, however, due to much higher entropies of activation. Several comparisons among the anionic nucleophiles are tabulated. The specific "ortho effect"^{73, 97c, 97e, 97f, 403} of nitro groups when the nucleophile is an amine has been demonstrated in halonitronaphthalenes: the rate ratio of 2-nitro- to 4-nitro-1-chloro- or -1-bromo-naphthalenes is 500–700 to 1 for piperidination in benzene solution.⁶⁵⁴ The ratio for the corresponding nitrohalobenzenes is 40–60 to 1.

The effect of variation of the leaving group can be seen in several series. For the unactivated halonaphthalenes (Table IX), the series $\text{I} \geq \text{Br} > \text{Cl}$ is observed. The relation varies in the quinolines (Tables X and XI) and nitronaphthalenes (Tables XII, XIII, and XVI), but generally there is very little difference between these halogens. In *activated* compounds (Table XI, lines 6, 26, and 30), iodine is the least reactive halogen substituent as a rule, and bromine is sometimes more reactive than chlorine. The latter relation occurs in some aminations mentioned^{261b, 278} in Section II, D, 2, b and as observed with the haloquinolines (Table X, lines 1 and 10). In amination (2–6 hr, 100–160°) of 2-halo- or 2-alkoxy-1,6-dinitro-, -1,8-dinitro-, or -1,6,8-trinitronaphthalenes, the methoxy and ethoxy compounds are distinctly less reactive and require longer times or higher temperatures^{655a} than do the halo analogs.

The kinetic data in Table XI on quinolines with substituents in the adjoining ring are primarily of interest here as a means of assessing the transmission of resonance and inductive effects. The data on the 1-oxide substituent in the same ring are the first to show its effect on nucleophilic substitution (cf. Table II, p. 270) and it is seen to produce stronger activation than a nitro group.¹³⁷ Reaction of the 4-haloquinoline 1-oxides with piperidine (100°) is accelerated 10–30-fold due to decreases of 4–10 kcal in the heats of activation with respect to the haloquinolines. The entropies of activation for the reaction of the *N*-oxides are all lower than those for the haloquinolines, reflecting a much greater solvation of the transition states of the *N*-oxides.¹³⁷ The same acceleration due to *N*-oxidation was observed^{643a} in the 4-substitution of 4-nitroquinolines with thioglycollate as nucleophile, but in this case E_A and ΔS^\ddagger were both increased. The activation may result from the more cationized hydrogen-bonded hydrate of the *N*-oxides (even in benzene solution due to their hygroscopic nature, cf. Section II, C) rather than from the *N*-oxide itself. These rates of piperidination of the 4-bromo- and 4-chloroquinoline 1-oxides are 1.6 times those of the 4-halo-1-nitronaphthalenes, and the heat of activation for the chloro *N*-oxide is 3.4 kcal lower than for its nitro analog. The activating effect of an *N*-oxide grouping in fluoroquinolines is greater than that of a nitro group and is transmitted to resonance-activated positions in the adjoining ring.^{255b}

The limited data⁶⁴⁷ available for 2,4-dichloroquinoline (Table X, line 9) show a substantially greater rate of methoxylation than for the 2- and 4-chloro analogs (Table X, line 6 and Table XI, line 2), as a result of activation (lowering of E_A) by the additional chlorine substituent. *Unequal* mutual activation (cf. Section III, B, 2) by these substituents is indicated by the rate ratio of 1.9:1 for 4- to 2-substitution in the dichloro compound and of 25:1 for the two monochloro compounds.

A moderate activating effect of chloro groups in the adjoining ring is clear from the data^{365,648,649} on 6-, 7-, and 8-chloro derivatives (Table XI, lines 10–14) of 4-chloroquinoline (Table XI, lines 2 and 4). Derivatives of the latter bearing alkyl³⁶⁵ and alkoxy groups⁶⁴⁹ (Table XI, lines 16, 17, 20–22) are only slightly deactivated compared to the effects of substituents^{643b} in the heterocyclic ring; alkylthio and arylthio derivatives^{648,649} (Table XI, lines 18 and 19) are slightly *activated*. Deactivation by the 6-methoxy group, which

can donate electrons to the 4-position (leaving group), is only slightly greater than that for the 7-methoxy group (electron donation to the quinoline-nitrogen). The resonance-activating 6-nitro group⁶⁴⁹ (Table XI, line 8) increases the rate of methoxylation by 300-fold, and the rate for 8-nitro-4-chloroquinoline was noted³⁶⁵ as being too fast for kinetic comparison at the temperature used for the haloquinoline. The effect of a nitro group in the adjoining ring can be assessed from the data on the nitronaphthalenes (Tables XII, XIII, and XVI).

Illuminati and co-workers^{655b} have recently reported additional data on the effects of benzo-ring substituents on the rate of methoxy-dechlorination of quinolines, quinoxalines, and cinnolines; the accelerations and decelerations reflect the decreases and increases in activation energy. Both 6- and 7-chloro groups increase the rate (by 6- and 10-fold, respectively) of 2-methoxy-dechlorination of 2-chloroquinolines and -quinoxalines. This difference and a similar one between the deactivating effects of 6- and 7-methoxy groups appears to be due to resonance electron donation from the 6-position. A 2- (or 4-)trifluoromethyl group on 4-(or 2-)chloroquinoline accelerates methoxylation by 68-75-fold and a 7-trifluoromethyl group on 2-chloroquinoxaline produces a 40-fold increase. The acetyl group in 4-acetyl-2-chloroquinoline causes a 20-fold faster rate of 2-methoxylation.

In their studies on the transmission of electronic effects through condensed-ring systems, Illuminati *et al.*^{599, 649} have begun to elucidate this important aspect of the reactivity of polycyclic azines. They have noted,⁵⁹⁹ as has Chapman,⁵⁵ specific variations in ΔS^\ddagger which affect the ratio of the reaction rates. The Erdman system of nomenclature which they use^{599, 649} seems unnecessarily obscure and cumbersome. We urge consideration of the "activation-numbering system" presented in Section IV, A, 1 as a unifying interrelation of the activating and deactivating effects of substituents as well as of ring-nitrogens. The terms homo-nuclear and hetero-nuclear for designating the relationship of substituents in naphthalenes as used by van Berk *et al.*⁵⁹⁸ is clear, but use of these terms^{599, 649} for substituted quinolines is misleading. The terms⁵⁹⁷ intranuclear and internuclear are used above in discussing activation. Comparison^{599, 649} of the effects of substituents in the two rings is based on *sigma* constants derived from *side-chain reactions* on different aromatic systems. Directly comparable data, when available, will be preferable since the effects in reactions one or two atoms farther removed seem certain to be

diminished in magnitude and the differences levelled out. One example of such diminution is the effect of a nitro group on the deacetylation (3-fold) of acetamidonaphthalenes compared to that on nucleophilic substitution (150-fold) of halonaphthalenes.⁵⁹⁸ It should be emphasized that the observed one-half to one-third decrease in the electronic effect on transmission from the adjoining ring⁵⁹⁹ is in the *sigma* constants and not in the reaction rates.

B. REACTION OF SIMPLE DERIVATIVES OF AZANAPHTHALENES WITH NUCLEOPHILES

1. General Aspects

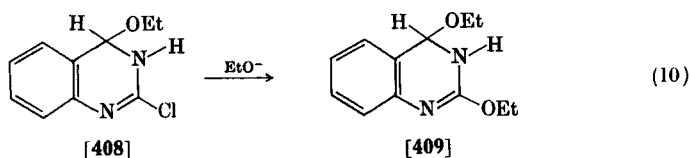
Qualitative and semi-quantitative indications from preparative organic chemistry demonstrate (a) activation by benzo-fusion to a monocyclic azine, (b) increased reactivity with more ring-nitrogens, (c) resonance activation \gg inductive activation, (d) intranuclear \gg internuclear resonance activation, (e) relatively poor resonance activation in the "2-Le-3-aza" and "4-Le-8-aza" orientations, and (f) accelerative "peri effects." The decrease in resonance activation on transmission from the adjoining ring is so great that the activation is sometimes underrated.^{606, 607, 656, 657} The special case of resonance activation in the 2,3-orientation is more properly attributed to limitations on the transition state imposed by the bicyclic system than to the ground state irregularity in bond lengths, known misleadingly as "bond fixation." Effects *a-f* reflect the relative energies of the bicyclic resonance structures (Schemes II-IV, Section IV, A, 1). The energy relations in the aminoazine cations (relative basicity⁶¹⁴ in equilibria) lead to generalizations comparable to effect *d* for quinolines, cinnolines, and quinazolines (e.g., 4- > 2- > 7- > 5-aminoquinazoline basicity), to effect *e* for isoquinoline (1- > 3-amino) and cinnoline (4- > 3-amino), and to *para* stabilization being greater than *ortho* stabilization for quinoline and quinazoline.

Evaluating relative reactivity at different positions by competitive displacement in polychloroazines requires the unjustified assumption that the chloro groups have a negligible or equal effect on each other. In a polychloro compound bearing a different kind of substituent, the activation or deactivation of the chloro groups is generally neither equal nor negligible, as already demonstrated.

One needs to interpret product data from preparative organic reactions with a great deal of reservation (cf. Section III, B, 1 and

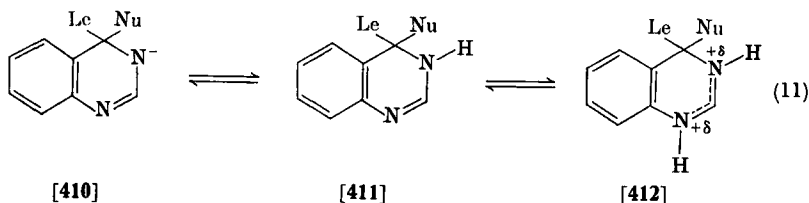
reference 498). In several instances which have been reinvestigated using better isolation procedures or different techniques, the "only product formed"^{477b} has been shown to be the minor one or one component of a mixture. A 30% yield of characterized product isolable in pure form still leaves the major product unknown unless one has ancillary data such as chromatography to show its true proportion in the total products. Its true proportion can also be obscured by the fact that the product generally most susceptible to further reaction will be that formed by attack at the most reactive position and therefore can be the main source of by-product (e.g., 4-Cl- > 2-Cl-quinazoline and the same relationship holds for their amination, alkoxylation, phenoxylation, thionation, and arylthiation products).

Specific alterations of the relative reactivity due to hydrogen bonding in the transition state or to a cyclic transition state or to electrostatic attraction in quaternary compounds or protonated azines are included below (cf. also Sections II, B, 3; II, B, 5; II, C; and II, F). *N*-Protonation is often reflected in an increase in ΔS^\ddagger and therefore the relative reactivity can vary with the significance of ΔS^\ddagger in controlling the reaction rate. Variation can also result from rate determination by the second stage of the S_NAr2 mechanism or from the intervention of thermodynamic control of product formation. Variation in the rate and in the reactivity pattern of polyazanaphthalenes will result when nucleophilic substitution [Eq. (10)] occurs only on a covalent adduct (408) of the substrate rather than on its aromatic form (400). This "covalent addition" is prevented by any 4-



substituent⁶⁵⁸ in quinazoline but not by substituents in other positions. Reaction via 412 is possible in certain acid-catalyzed reactions [Eq. (11)] or 411 can be formed by nucleophilic attack on the 3-protonated quinazoline. "Covalent hydration" has been observed also in 1,3,5-, 1,3,6-, 1,3,7-, 1,3,8-, and 1,4,6-triazanaphthalenes and in 1,3,5,8- and 1,4,5,8-tetraazanaphthalenes (pteridines).^{614, 659} "Covalent additions" to mono- and poly-azines have been observed with cyanide,

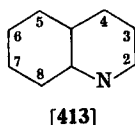
bisulfite, and hydride ions, with ammonia, water, and carbanions of active methylene compounds^{11b, 150, 151}; cf. mechanism of Bucherer interconversion of naphthols and naphthylamines. "Covalent hydration" occurs with 3- and 8-nitro-1,6-naphthyridine but not with 1,6-naphthyridine itself, 3-nitro-1,5-naphthyridine nor 4-nitroisoquinoline (analogous to quinazoline which readily hydrates).^{660a}



The preparative organic chemistry pertinent to the degree of reactivity and to the relative reactivity toward nucleophiles is given below under each ring system, arranged in order of increasing ring-nitrogen content and in order of the azanaphthalene numbering.

2. Monoazanaphthalenes

a. *Quinoline (1-Azanaphthalene)*. There are seven different positions (413) for a leaving group to occupy in this bicyclic monoazine; three are subject to intranuclear activation⁵⁹⁷ and four to internuclear activation.⁵⁹⁷ Kinetic comparison of the halo derivatives (Section IV, A, 1 and Tables X and XI) gives the order of the reaction rate $4- > 2- \gg 7- > 3- > 6- > 5$ -position, the reactivity in general depending



on the relative lowering of the energy of activation. Resonance activation at the 4- and 2-positions is greatest, at the 7-position is moderate, but at the 5-position resonance activation is very poor due to the relatively high energy of the *ortho,ortho*-quinoid transition state (345). Internuclear activation at the 7-position is much less, by several orders of magnitude in the reaction rate, than intranuclear activation. Inductive activation at the 3- and 6-positions is in proportion to the distance between the azine-nitrogen and the leaving group. The

inductively activated 8-derivatives are sometimes higher in the order of reactivity due to an accelerative "peri effect" (hydrogen bonding in the transition state of aminations, etc.). 6- and 8-Bromoquinolines are so poorly activated for displacement that, with methanolic methoxide (125°), a reductive side-reaction yielding quinoline predominates.⁶³⁷ The 7-bromo isomer has been methoxylated^{660b} (250°, 7 hr), and the 7-chloro and -bromo compounds react^{660b} with aqueous dimethylamine (250–290°, 8 hr).

2-Chloroquinoline (**401**) reacts well with potassium fluoride in dimethylsulfone while its monocyclic analog 2-chloropyridine does not.⁶⁶¹ Greater reactivity of derivatives of the bicyclic azine is evident also from the kinetic data (Table X, p. 336). 2-Chloroquinoline is alkoxyated by brief heating with methanolic methoxide or ethanolic potassium hydroxide^{662,663} and is converted in very high yield into the thioether by trituration with thiocresol (20°, few hrs).⁶⁶⁴ It also reacts with active methylene carbanions⁶⁶⁵ (45–100% yield). The less reactive 3-halogen can be replaced under vigorous conditions (160°, aqueous ammonia–copper sulfate), as used for 3-bromoquinoline⁶⁶⁶ or its *N*-oxide.⁶⁶⁷ 4-Chloroquinoline (**406**) is substituted by alcoholic hydrazine hydrate (80°, < 8 hr, 20% yield)⁶⁶⁸ and by methanolic methoxide (140°, < 3 hr, > 90% yield).^{283a} This apparent reversal of the relative reactivity does not appear to be reliable in the face of the kinetic data (Tables X and XI, pp. 336 and 338) and the other qualitative comparisons presented here.

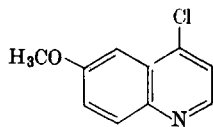
The relations 4- > 2-position in rate and 4- < 2-position in E_A will apparently apply to reactions with anions, but the reverse relation is observed in piperidination,^{486a} presumably due to 2-substitution being favored by hydrogen bonding in the zwitterionic transition state (cf. **47**, **59**, and **277**) or by solvent-assisted proton removal from the intermediate complex (**235**). Substitutions of polychloroquinolines^{249, 427, 669} (in which there is a combined effect of azine-nitrogen and *unequal* mutual activation of the chlorine substituents) also show 4- > 2-position in reactivity; contrary statements^{631, 670} are documented by these same references. Examples are cited below of the relation 2- > 4-position when a protonated substrate or a cyclic transition state is involved.

2,4-Dichloroquinoline with ethanolic potassium hydroxide (80°, 2 hr) gave⁴²⁷ equal amounts (31 and 32% yields) of 4- and 2-ethoxylation. In an earlier paper,⁶⁶⁹ only the 2-ethoxy product, in unspecified yield,^{477b} was reported. The reaction of the dichloro compound with

anilines in glacial acetic acid gave 2-substitution products³¹³ which were isolated in only 34–50% yield.^{477b} This type of amination is expected to be acid-catalyzed by bifunctional catalysts (acetic acid and the autocatalytic anilinoquinoline products) and a marked increase in reactivity at the 2-position will therefore result from the cyclic transition state²¹⁸ (cf. Section II, C).

Reaction of 2,4,7-trichloroquinoline with sodium methoxide (65°, 30 min) yielded²⁴⁹ an equal mixture of 2,7-dichloro-4-methoxy- (40%) and 4,7-dichloro-2-methoxy-derivatives (31%). The activating effect of the chloro groups is evident from the "inertness"^{283a} of 4-chloroquinoline to methoxide ion at 65°. Alteration of the relative reactivity by cationization of the azine ring is again noted here in the acid-catalyzed hydrolysis (dilute HCl, 100°, 1.5 hr) of the trichloro compound to give 72% of the 2-hydroxylation product.²⁴⁹ Similarly, acid-hydrolysis of the alkoxy group proceeds much more readily in 2-ethoxy-4-chloro- than in 4-ethoxy-2-chloro-quinoline.⁴²⁷

Alteration of the relative reactivity of the ring-positions of quinoline is expected and observed when cyclic transition states can intervene. Quinoline plus phenylmagnesium bromide (Et₂O, 150°, 3 hr) produces the 2-phenyl derivative (66% yield)⁵⁹⁶; phenyllithium gives predominantly the same product along with a little of the 4-phenylation product.⁵⁹⁴ Reaction of butyllithium (Et₂O, –35°, 15 min) forms 2-butylquinoline directly in 94% yield.⁶⁷¹ 2-Aryl- or 6-methoxyquinolines give addition at the 2-position with aryllithium reagents,^{595, 672} and reaction there is so favored that appreciable substitution (35%) takes place⁵⁹⁵ at the 2-position even in the 4-chloroquinoline **414**. Hydride reduction at the 2-position of quinoline predominates.^{592b} Reaction of amide ion at the 2-position via a cyclic

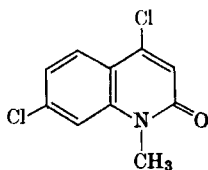


[414]

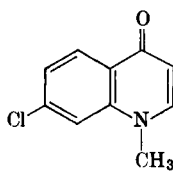
transition state is postulated. Consistent with this postulate is 2-amination (80% yield) of quinoline with barium amide while potassium amide in liquid ammonia produces 55%:10% yields of 2- to 4-amination products.⁶⁷³ High yields (99% and 80%, respectively)

of the 4-amination products of 2-phenylquinoline⁵⁹³ and 2-carboxyquinoline⁶⁷⁴ result from reaction with potassium amide, but some 2-substituents (methoxy and sulfonate) are displaced⁶⁷⁴ (70–80% yields). The deactivated 2-position in 6- and 8-methoxyquinoline also reacts (80%) as readily as the parent azine.⁶⁷⁴

Increased reactivity toward amines and hydroxide ion is observed upon quaternization, e.g., 1-methyl-4,7-dichloroquinolinium ion.⁶⁷⁵ The effect of the positive charge in favoring substitution (cold alkali) at the adjacent 2-position is so great that about 20% of the 2-hydroxylation product (**415**) was isolated in addition to 35% of the compound (**416**) formed by displacement of the highly reactive 4-chloro group.



[415]



[416]

The formation of 2-quinolones from quinoline quaternary salts is well known,⁶⁷⁶ but usually a good leaving group in another strongly activated position is not present. 1-Alkyl- and 1-aryl-quinolinium compounds undergo facile nucleophilic displacement of halo groups with halide or hydroxide ions, carbanions, or amines and hydrazines, and of amino groups with hydroxide ion.^{675, 677} Quinoline *N*-alkyl quaternary compounds form 2-addition products in 40–85% yield with various Grignard reagents⁶⁷⁸ and in 5–20% yield with dialkylcadmium,⁶⁷⁸ but 4-addition products are formed with cyanide ion⁶⁷⁹ (90% yield) and anions of nitromethane⁶⁸⁰ (40% yield), malononitrile⁶⁸¹ (10% yield), and ethyl cyanoacetate⁶⁸¹ (25–35% yield). A marked increase in reactivity due to cationization is demonstrated by the instantaneous reaction (100% yield) of 4-chloro-1-methylquinolinium ion with malononitrile anion.⁶⁸¹ Product control in some of the reactions of such quaternary salts may depend on the relative oxidizability of the adducts or on stabilization due to interaction of the nucleophile moiety with the *N*-substituent in the transition state or intermediate complex. The latter may well control the 2-addition of cyanide ion to *N*-acylquinolinium compounds.⁶⁸² It is also possible that product formation in some reactions of quaternary salts is

thermodynamically controlled. Steric hindrance due to the combined bulk of the *N*-substituent and the nucleophile is evident in the reactions with organometallics.⁶⁷⁸

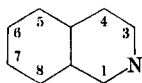
Resonance activation of a leaving group in the benzo-ring is less by several powers of ten (in rate) than intranuclear⁵⁹⁷ resonance activation, but the reactivity of such derivatives is greater than that in the naphthalene analogs (cf. Section IV, A, 2). In methoxylation of 4,5-dichloroquinoline⁶⁸³ (poor resonance activation of the 5-position) or of 2,4,7-trichloroquinoline,²⁴⁹ monosubstitution at the 5- or 7-positions was not observed in the products isolated but possibly could be detected by chromatography. 4,7-Dichloroquinoline reacts with phenylacetonitrile carbanion predominantly^{477b} at the 4-position.⁶⁸⁴ The *N*-methyl quaternary salt of this dichloro compound reacts with amines first at the 4-position (20°, 16 hr) and then at the 7-position (100°, 5 hr) to give 4,7-diamino derivatives (55–70% yields).⁶⁷⁵ 4-Chloro-, 4-ethoxy-, and 4-oxo-7-chloroquinolines react (reflux, 8 hr) with *p*-tolylmercaptan at both positions (35–90% yields), and, in the latter case, substitution of the 7-chloro group occurs first.^{247, 248a, 305, 685a} 7-Alkoxylation (65°, 8 hr, 50% yields) and acid-catalyzed 7-anilination (50% yields) of 7-chloro-2-methyl-4-oxoquinoline have been described.^{685b} Phenylhydrazine (in ethanolic HCl, 78°, 30 min, 80% yield) gives 7-substitution of 7-chloro-4-phenylhydrazinoquinoline.^{685c} Preparative replacements (with CN, NH₂, OH) are reported⁶⁸⁶ for 8-chloroquinoline.

The protonated quinoline ring confers sufficient activation for easy hydrolysis (60–100°, 0.2–1 hr) of 2- and 4-alkoxy groups^{427, 663, 687}; the other less reactive alkoxyquinolines are probably *dealkylated* by an aliphatic *S_N2* mechanism with hot concentrated acids rather than being *hydrolyzed*. Although 4-chloroquinoline (**406**) is inert^{283a} to methoxide at 65° (6 hr), it reacts under acid-catalysis with aniline (in dilute HCl, 60°, 30 min, 90% yield) and phenoxide ion (in phenol, 95°, 6 hr, nearly quantitative yield).^{283a} The 4-phenoxy derivative undergoes acid-catalyzed amination with ammonium acetate (195°, 15 min, 100% yield).^{283a} Replacement of the 4-hydroxy group in 4-hydroxy-2-quinolone and its 7-chloro derivative with alkylamines or anilines (latter under acid-catalysis) proceeds in 70–90% yield (170–180°, 18–12 hr).^{312a} Summarized in the reviews cited are substitutions of 2-chloro groups with phenylmagnesium bromide or butyllithium⁶⁸⁸ and with various nitrogen, oxygen, and sulfur nucleophiles^{689, 690} and hydrolysis and transamination of 2-amino groups.⁶⁸⁸

The effect of substituents on the reactivity of haloquinolines is illustrated in the kinetic data of Tables X and XI (pp. 336 and 338). A 2- or 4-methoxy substituent in 2- or 4-chloroquinoline⁶⁴⁷ changes the order of reactivity toward methoxide ion ($2- > 4\text{-Cl}$ by 3-fold in rate). The greater reactivity in aminations of 2-chloro-4-oxo- and 2-chloro-4-alkoxy-quinolines than of their 4-chloro isomers is presumed to be also due to hydrogen bonding in the zwitterionic transition states of the former. Aminations, hydrolyses, and methanolyses of 5-, 6-, or 8-nitro derivatives of 2-chloro-, 4-chloro-, or 4-phenoxy-quinolines proceed well under conditions not vigorous enough for the des-nitro compounds^{283a, 691}; the 8-nitro compounds are somewhat more reactive than the 5-nitro analogs.

The nucleophilic substitution of quinoline as affected by cationization and hydrogen bonding is discussed in Section II, C, by the leaving group and other substituents in Sections II, D and II, E, respectively, and in Section III, A, 2, and by the nucleophile in Section II, F.

b. *Isoquinoline (2-Azanaphthalene)*. No comparison of the seven possible monosubstituted derivatives (417) has been made in a kinetic study or a semi-quantitative comparison. The relative reactivity of the ring-positions is estimated in Section IV, A by means of the kinetic data on 2-nitronaphthalenes (Table XIII, p. 345) and on 1- and 3-chloroisoquinoline (Table XIV, p. 348). The latter reacts with



[417]

ethoxide ion and alcoholic piperidine 10^5 -fold less rapidly than does 1-chloroisoquinoline or 2-chloroquinoline. This relation has led to statements^{55, 618} grossly underestimating the activation. However, this *relatively* poor resonance activation in the 2,3-orientation (352) of the ring-nitrogen and leaving group (cf. Section IV, A, 1) still increases the reaction rate 10^5 -fold relative to that of 2-chloronaphthalene. On the basis of the nitro analogs, it is more effective than internuclear resonance activation⁵⁹⁷ and much more effective than inductive activation in either ring.

1-Chloroisoquinoline (404) reacts well with methanolic methoxide (65° , 2 hr, 87% yield)⁶⁹² or alkoxides (80° , 3 hr)^{693, 694} and with carbanions of active methylene compounds⁶⁸⁵ (45–100% yields).

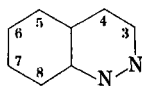
Reaction of 1-chloro-4-bromoisquinoline with methanolic methoxide (78° , 3 hr) gives 1-methoxy-4-bromoisquinoline (80% yield)⁶⁹⁵; 1,3-dichloroisquinoline⁶⁹⁶ and 1,4-dichloro-3-methylisquinoline⁶⁹⁷ also give 1-methoxy-dechlorination. Other indications of the greater reactivity of the 1-position are 70–85% yields of the product of 1-amination of unsubstituted isoquinoline with amide ion^{694, 698, 699} and 70–90% yields of 1-alkylation and -arylation products with Grignard reagents^{596, 700} and alkylolithiums.⁷⁰¹ *N*-Alkylisoquinolinium compounds also react with Grignard reagents (50–80% yields) and dialkylcadmiums (5–20% yields) at the 1-position.^{678, 700} 1-Chloroisquinoline reacts well with anilines and alkylamines under conditions giving no reaction with the 3-chloro isomer.³⁸³ 1,3-Dichloroisquinoline reacts under bifunctional acid-catalysis (AcOH, 120° , 3 hr) with 4-chloroaniline to give a 2:3 mixture of mono- and disubstitution products.³⁸³

4-Bromoisquinoline can be aminated under vigorous conditions (concentrated NH_4OH , 165° , 16 hr),^{699, 702} but attempted methoxylation (methanolic methoxide, 235° , 7 hr) gave isoquinoline⁶⁹⁹ (50% yield) via the reductive reaction observed with 6- and 8-bromoisquinoline.⁶³⁷

The accelerative effect of quaternization on the reactivity of 1-halo groups toward water, alcohol, or ammonia has been reported.²³¹

3. Benzodiazines (1,2-, 1,3-, 1,4-, and 2,3-Diazanaphthalenes)

a. *Cinnoline* (1,2-Diazanaphthalene). A kinetic comparison of ethoxylations of 4-chlorocinnoline and a few other chlorobenzodiazines (Table XV, p. 352) is available.⁵⁵ Cinnoline has six ring-positions (418) with different activation. The relationship of cinnoline to its



[418]

azalogs in reactivity is also shown in Scheme VIII (p. 355): in ethoxylation, 4-chlorocinnoline (407) reacts twice as fast as 1-chlorophthalazine (403), half as fast as 2-chloroquinoxaline (402), and 10^4 times as fast as 4-chloroquinoline (406). "4-Chlorocinnolines are characterized as a group by their extreme reactivity; 4-chloroquinoline, which is commonly regarded as a classical illustration of a heterocyclic compound with a reactive chlorine atom, is a very stable compound when

compared with most 4-chlorocinnolines.⁷⁰³ 4-Chlorocinnoline decomposes on standing⁷⁰³ and is very rapidly hydrolyzed by acid.²⁴⁶ In preparative organic reactions, 3-substituted cinnolines are less reactive than the 4-isomers; the 5-, 6-, 7- and 8-isomers are still less reactive but have been little studied.

Toward methanolic methoxide at 20°, 4-chlorocinnoline (1 hr) is less reactive than 4-chloroquinazoline (instantaneously), while 4-chloroquinoline is inert even at 65° (6 hr).^{238a} In phenoxylation (50°, > 1 hr) of 4-chlorocinnoline, in hydrolysis of the 4-chloro (autocatalytic with water, 100°, 15 min) or of the 4-phenoxy derivatives (dilute acid, 100°, 30 min), and in aminolysis (bifunctional acid-catalyst and reagent, molten ammonium acetate, 195°, 9 min) of 4-phenoxy-cinnoline, these cinnolines are more reactive than the 4-quinolinyl and less reactive than the 4-quinazolinyl analogs.^{283a} A similar relationship holds true for nucleophilic transesterification (80°, 15 min) of 4-methoxycinnoline with alcoholic ethoxide or isopropoxide (60% yields): 2- and 4-quinazolines > 4-cinnoline ~ 1-phthalazine > 2-quinoxaline > 2-quinoline ~ 1-isoquinoline.⁷⁰⁴ Activation from the adjoining ring makes the 6- or 8-nitro derivatives of 4-phenoxy-cinnoline "about as reactive" as 4-phenoxyquinazoline.^{283a} Hydrazine in alcohol (20°, 4 days) aminates 4-chlorocinnoline in 90% yield, but 4-chloroquinazoline reacts at once with heat evolution⁶⁶⁸; a similar difference (the cinnoline is unreactive) is found with aqueous ammonia.²⁴⁶ 4-Chlorocinnoline also reacts (80°, 45–80% yields) with carbanions of various active methylene compounds less vigorously than does the haloquinazoline.^{665, 705, 706}

The *relatively* poor resonance activation of the "2-Le-3-aza" orientation in bicyclics (cf. Section IV, A) is illustrated by nucleophilic substitutions below. Vigorous conditions are required for methoxylation (110°, 17 hr, quantitative yield) of 3-bromocinnoline and for amination (aqueous ammonia, copper sulfate, 20 hr, high yield) of 3-bromo- (at 130°) or of 3-chloro-derivatives (at 165°).^{707a} 3,4-Dichlorocinnoline gives predominantly 4-substitution⁶⁶⁸ in hydrazination (90% yield, 20°, 4 days in alcohol), amination (70% yield, 150°, 22 hr in alcohol), and hydroxylation (50% yield, 150°, 22 hr, aqueous ammonia). The poorer-leaving phenoxy group in 3-chloro-4-phenoxy-cinnoline, is displaced with ammonium acetate (160°, few mins, 60% yield).⁶⁶⁸

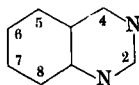
The activation in cinnolines is sufficient to enable nucleophilic substitution of poor leaving groups such as amino and phenoxy

groups, generally with the assistance of acid catalysis. The preparation of 4-aminocinnolines from 4-chlorocinnolines by way of 4-phenoxy compounds is preferable in yield, but not in rate, to the direct route.^{707b}

The expected predominance of substitution in the azine-ring occurs in hydrazination (20°, 4 days in alcohol) of 4,6-dichloro- (50% yield) and of 4-chloro-6-bromo-cinnolines (quantitative yield) and in hydroxylation (150°, 22 hr, aqueous ammonia) of the former.⁶⁶⁸ Acid-catalyzed displacement of halogen in the other ring occurs rather readily with halide ion under conditions often used for replacing an oxo with a halo group. Conversion of 6-bromo- and 3-bromo-4-chlorocinnolines into the dichloro analogs with phosphorous oxychloride (95–135°, 2 hr, 30–100% yields) has been studied^{708, 709}; the analogous quinolines are only very slightly reactive. A rapid replacement (95°, few min) of the nitro group in 4,7-dichloro-6-nitrocinnoline has also been reported.^{710a} Resonance activation from the adjoining ring contributes to the facile conversion of 4-chloro-3-methyl-6-nitrocinnoline into the 4-methoxy analog and the easy hydrolysis of the latter.^{283a} 6-Halogeno-4-cinnolinones yield 6-mercapto-4-cinnolinethiones with phosphorus pentasulfide in boiling pyridine (but not toluene).^{710b}

The effect of the leaving group and of other substituents on nucleophilic substitution of cinnolines is discussed in Sections II, D and II, E, respectively.

b. *Quinazoline (1,3-Diazanaphthalene)*. Of the six different ring-positions (419), only the 2- and 4-positions have been studied extensively in nucleophilic substitutions. 4-Substituted quinazolines are the



[419]

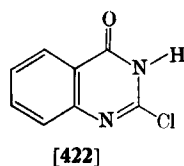
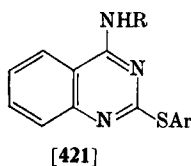
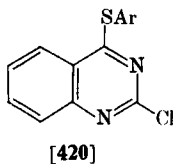
most reactive of the diazanaphthalene derivatives due to intranuclear resonance activation by ring-nitrogens in the optimal 1,3-arrangement. Reactions at the 4-position proceed more rapidly than at the 2-position for the same reasons as they do in pyrimidine plus the unfavorable "2-Le-3-aza effect" (352, 398) in bicyclics. In piperidination (Table XV, p. 352), 4-chloroquinazoline (405) reacts 10⁴-fold faster than the 2-isomer, 10⁸-fold more rapidly than 1-chloroisoquinoline (404), and 10⁵-fold faster than 1-chlorophthalazine (403), the

relations (Scheme VIII, p. 355) being determined primarily by the much lower activation energy for **405**. 2-Chloroquinazoline (**400**) is more reactive, as expected, than the quinoxaline **402** in piperidination, but the reverse relation in ethoxylation is anomalous, with E_A for the quinazoline being higher. In 2-4-disubstituted quinazolines, the difference between the reactivity at the 4- and 2-positions will be accentuated by the substituents. A variety of combinations of leaving group and nucleophile in such derivatives all show the 4-position more reactive than the 2-position.

4-Chloroquinazoline and methanolic methoxide^{283a, 662, 711} or alcoholic hydrazine⁶⁶⁸ react (25°) quantitatively, exothermically, and much more rapidly than do the 4-cinnolinyl or the still less reactive 4-quinolinyl analogs. The same order of reactivity holds in the following nucleophilic substitutions (conditions for quinazolines): hydrolysis (water, 100°, 15 min, 100% yield), methoxylation (MeO^- , 20°, 5 min, 80% yield), and phenoxylation ($\text{C}_6\text{H}_5\text{O}^-$ in phenol, 50°, 5 min, 95% yield) of 4-chloroquinazoline; acid hydrolysis of 4-amino (1*N* HCl, 100°, 0.5 hr, 75% yield) or 4-phenoxy-quinazoline (0.02*N* HCl, 100°, 1 hr, 100% yield).^{283a} In acid-catalyzed anilation of the 4-chloro derivatives, the differences are telescoped due to the increased reactivity. In bifunctional acid-catalyzed amination of the 4-phenoxy derivatives, the quinazoline was the more reactive (190°, 9 min, 100% yield).^{283a} In nucleophilic transesterification (80°, 0.2 hr) of methoxy derivatives with ethoxide or isopropoxide ions, the 4-quinazolinyl ether was more reactive than the 2-quinoxalinyl ether; the 2-quinolinyl and 1-isoquinolinyl analogs are unreactive.⁷⁰⁴ The degree of reactivity of 4-quinazolinyl derivatives is demonstrated by the facile displacement of the 4-cyano group with Grignard reagents as well as with methoxide ion (65°, 15 min, 60% yield), butylamine (20°, 80% yield) or alkali (20°, 15 min, 100% yield) or active methylene carbanions^{265b, 266a-c}; by displacement of 4-thioxo⁷¹² (100°, 20 min), 4-oxo (200°, 24 hr)⁷¹³ or 4-methoxy groups (140°, 16 hr)⁷¹³ with amines or ammonia; by substitution of a 4-chloro group with ammonia (20°, 16 hr, 70% yield)⁷¹⁴ or with alcoholic hydrosulfide (20°, rapid, quantitative yield)⁷¹⁵; by the facile acid-hydrolysis of 4-dialkylamino groups (some are as reactive as a 4-chloro group).⁷¹⁴ 4-Chloro-, 4-cyano- and 4-methoxy-quinazolines are more reactive toward amines, hydrazine, alkoxide, and aryloxide,^{265b} toward acid-hydrolysis,^{662, 716} and toward active methylene carbanions^{665, 717} than are the 2-quinazolinyl analogs.

The inclination of quinazoline derivatives toward nucleophilic substitution is so great that 2- or 4-chloro compounds bearing a 2- or 4-deactivating group (amino or alkoxy) still react readily with alkoxides (80°, 10 min), amines (100–150°, 2 hr), and hydrazine (100°, 1.5 hr),^{718–721} in high yield. 2-Cyano-4-methoxyquinazoline, prepared *in situ* from the 4-chloro analog, reacts readily with methanolic methoxide (65°, 30 min, 80% yield) at the 2-position.^{722a} 2-Chloroquinazoline bearing a 4-oxo or 4-piperidino group reacts readily (78°, 1 hr, 98% yield) with sodium azide^{722b} or with alkylamines.^{722c}

In 2,4-disubstituted quinazolines, the 4-position reacts fastest with nucleophiles, generally even when the 4-substituent is a poorer leaving group. 2,4-Dichloroquinazoline undergoes mono-substitution at the 4-position with alcoholic alkoxides (25°, 2 hr, 80–98% yield),^{306b, 721, 723} phenolic phenoxide (20°, 16 hr, 50% yield),⁷²¹ aqueous hydroxide (30°, 3 hr),^{306b, 724} alcoholic methylmercaptide (20°, exothermically),⁷²⁴ alkylamines (20°, 10–60 min, 100% yield)^{722c, 724} or arylamines (20°, 24 hr),^{284a} or arylmercaptide ion (28°, 4 hr, high yield).^{284a} 2,4-Dialkoxy- or 2,4-diaryloxy-quinazolines react at the 4-position with hydroxide (65–80°, 5 hr, 90% yield)^{719, 720} or alkoxide ion (20°, 16 hr, or 95°, 1 hr, 100% yield).^{306b, 719} With sodium and ethanol⁷¹⁹ the 4-oxo derivative is formed from the dialkoxy derivatives by *hydrolysis*, not by dealkylation with alkoxide ion; reactions postulated as being of the latter type have always turned out to be hydrolyses on further study. Quinazoline-2,4-dithione, its 6-amino derivative, and the 5-alkyl analogs aminate at the 4-position.³²⁸ 4-Arylamino-2-chloroquinazoline yields the bis-alkylamino derivative^{284a} with 2-diethylaminoalkylamine (120°, 3.5 hr), possibly via autocatalysis. Displacement of the poorer leaving group in 4-arylthio-2-chloroquinazoline (**420**) yields the 4-oxo-2-chloro analog with hydroxide ion (80°, 4 hr),^{284a} but, with a 2-diethylaminoethylamine (80°, 2 hr in alcohol), the 4-alkylamino-2-arylthio analog (**421**) results^{284a} from the combined effect of relative reactivity of the 4- vs. the 2-position and the high nucleophilicity of the liberated mercaptide. 2-Chloro-4-phenoxyquinazoline with ethoxide or methoxide ion



cleanly reacts (20°, 16 hr) first at the 4-position.^{306b} The sequence in dimethoxylation of the 2-chloro-4-ethoxy derivative is unknown,^{306b} but nearly quantitative hydrolysis (80°, 1 hr, alcoholic HO⁻) of it to give **422** has been demonstrated.⁷¹⁹ 2,4-Dimorpholinoquinazoline is substituted at the 4-position with hydrazine (130°, 2 hr, 93% yield).^{722b}

Acid catalysis can produce a change in the relative reactivity as well as a dramatic increase in the reaction rate. 2-Chloro-4-ethoxyquinazoline reacts with excess ammonia at the 4-position, but, with aniline under acid catalysis, substitution takes place at the 2-position.⁷²⁴ Autocatalytic methanolysis (20°, 15 min, 91% yield) of 4-chloroquinazoline (**405**) proceeds rapidly, but the chloro-azine can be recrystallized from slightly *alkaline* methanol.⁷¹⁴ The instability of 2,4-dichloroquinazoline to atmospheric moisture is the result of similar autocatalysis. The cation of quinazoline and certain 2-substituted derivatives is unique among the diazanaphthalenes in that it undergoes nucleophilic addition of water at room temperature.^{11b, 150, 614, 725} In quinazoline (but not in its derivatives), the most basic ring-nitrogen is at the 3-position,⁶⁵⁸ and, consequently, addition of HSO₃⁻, HCN, and N₂H₄ (hydrogen bonded to N³) takes place at the 4-position.¹⁴⁵ Substitution of hydrogen results with the last two reagents at 70° and 20°, respectively.

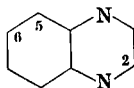
Organometallic reagents and alkali metal amides can react via a cyclic transition state (Section II, B, 5) beginning with electrophilic attack at the most basic ring-nitrogen. As a result, sodamide (in dimethylaniline, 145°, 2 hr) yields the 4-amino derivative¹⁴⁵ (40% yield^{477b}), and methyl- or phenyl-magnesium iodides give the 4-adduct quantitatively.^{145, 726}

Chlorine in the benzo-ring may undergo substitution in trace amounts, but the major reaction of 2,4,6- and 2,4,7-trichloroquinazolines with aqueous 2-diethylaminoethylamine (20°, 16 hr) is in the azine ring.⁷²⁷ Resonance activation from a 6- or 8-nitro group in the benzo ring of 4-alkylmercaptoquinazolines causes a nucleophilic ring-opening (cf. Section IV, B, 5, c) which does not occur in the 7-nitro or the des-nitro analogs.⁷²⁸

Quinazoline derivatives are used as examples in discussion of the effect of hydrogen bonding or cationization (Section II, C), of the leaving group (Section II, D), and of other substituents (Section II, E).

c. *Quinoxaline (1,4-Diazanaphthalene)*. Of the three different ring-positions (**423**) in this bicyclic azine, only the 2-position has been compared⁶⁵ in nucleophilic substitutions with those in other azanaph-

thalenes (Table XV and Section IV, A, 2). Inductive activation by the additional ring-nitrogen is evident in the 10^2 -fold greater rate of piperidination and the 10^4 -fold greater rate of ethoxylation of 2-chloroquinoxaline than of 2-chloroquinoline (Scheme VIII, p. 355).



[423]

2-Quinoxaliny, 4-cinnoliny, and 1-phthalaziny derivatives, which are all activated by a combination of induction and resonance, have very similar kinetic characteristics (Table XV, p. 352) in ethoxylation and piperidination, but 2-chloroquinoxaline is stated⁷²⁹ (no data) to be more slowly phenoxylated. In nucleophilic substitution of methoxy groups with ethoxy or isopropoxy groups, the quinoxaline compound is less reactive than the cinnoline and phthalazine derivatives and more reactive than the quinoline and isoquinoline analogs.⁷⁰⁴ 2-Chloroquinoxaline is more reactive than its monocyclic analog, 2-chloropyrazine, with thiourea⁷³⁰ or with piperidine (Scheme VI, p. 350).

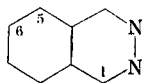
The degree of reactivity of quinoxaline derivatives is indicated by the methoxylation⁷³¹ (65° , 2 hr, 92–98% yield) and amination^{732, 733} (alcoholic amines, 150° , 7 hr, 70–99% yields) of 2-chloroquinoxaline and its 3-methyl homolog. A 2-methylthio group was less reactive than a chloro group toward amines, while a 2-methylsulfonyl substituent was more reactive (2*N* alkali, 95° , 15 min, 97% yield).⁷³³ 2,3-Dichloroquinoxaline can be monomethoxylated⁷³¹ at 65° in high yield, but it is also readily (65° , 1 hr, 100% yield) dimethoxylated⁷³⁴ and diethoxylated (80° , 3.5 hr, 80% yield).⁷³² The dichloro compound can be mono-substituted with alcoholic ammonia (80° , 20 hr, 70% yield), alkylamines (0 – 15° , 5 hr, high yields), or anilines (in dilute acid, 100° , 24 hr); more vigorous treatment with aniline (185° , 10 min) gives disubstitution.³⁸³

A search has not been made for products of displacement of halogen from the benzo-ring in polyhalo compounds, but it is clear that the major mono-substitution occurs in the azine ring. For example, 2,6- and 2,7-dichloroquinoxalines give 70–80% of the 2-amination product with β -diethylaminoethylamine (150° , 2 hr) or γ -(1-piperidyl)-propylamine (220° , 2 hr).⁷³⁵ 2,3,6-Trichloroquinoxaline gives with

the latter (80°, 18 hr in ethanol) 80% of the mono-amination product (1:3 ratio of 2- to 3-substitution).^{383, 735} With methanolic methoxide (65°, 1.5 hr), it gives 2,3-dimethoxylation (95% yield),⁷³⁵ and with glacial acetic acid (100°) or excess 4-chloroaniline (140°) 2,3-disubstitution³⁸³ also results.

The effect of nuclear substituents on nucleophilic substitution of quinoxalines is included in Section II, E, and in section III, A, 2.^{655b}

d. *Phthalazine* (2,3-Diazanaphthalene). Kinetic comparison of phthalazine (**424**, three different ring-positions) reactivity with that



[424]

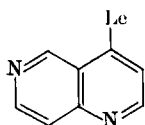
of other azines is summarized in Scheme VIII (p. 355) and Table XV (p. 352). In ethoxylation or piperidination, 1-chlorophthalazine (**403**) has a slower rate and a higher E_A than the 4-cinnolinyl (**407**) and 2-quinoxalinyll analogs (**402**). With piperidine, it reacts 10^5 -fold less rapidly than 4-chloroquinazoline (**405**). Compared to its azalog, 1-chloroisoquinoline (**404**), it has lower activation energies and reacts faster in piperidination (10^2 -fold) or ethoxylation (10^3 -fold). 1-Chlorophthalazine is more reactive than 4-chloroquinoline (**406**) and less reactive than 4-chloroquinazoline to autocatalytic methanolysis (20°) or to amination (20°, aqueous ammonia).²⁴⁶ In nucleophilic transesterification, 1-methoxyphthalazine is considerably more reactive than 2-methoxy-4-methylquinoline or 1-methoxyisoquinoline, and somewhat more reactive than 2-methoxy-3-methylquinoxaline.⁷⁰⁴

1-Chlorophthalazine is quite reactive to many basic nucleophiles but reacts sluggishly with aqueous or alcoholic alkali.²⁴⁶ In contrast, it is very rapidly hydrolyzed by warm, concentrated hydrochloric acid as are its diazine isomers.²⁴⁶ In hydrolysis with very dilute acid or with water, it forms some phthalazinone but mostly the self-condensation product²⁴⁶ which hydrolyses to give 2-(1'-phthalazinyl)-phthalazin-1-one (70% yield). Such self-condensations in diazanaphthalenes and in monocyclic azines are always acid-catalyzed (Sections II, C and III, B). With methanolic methoxide, 1-chlorophthalazine (65°, few mins),⁷³⁶ its 7-methoxy analog⁷³⁷ (20°), and 1,6- and 1,7-dichlorophthalazines⁷³⁷ (20°) readily undergo mono-substitution.

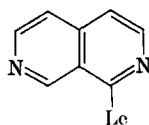
1,4-Dichlorophthalazine can be readily mono- (80°, 30 min) or di-substituted (80°, 30 min, excess nucleophile) with aniline³⁸³ or methoxide (65°).⁷³⁸ Attempted displacement (200°, 20 hr) of methoxy groups from 1,4-dimethoxy- or 1-methoxy-4-oxo-phthalazines with morpholine or aniline gave at least 70–90% demethylation⁷³⁸ via aliphatic S_N2 attack at the methyl carbon. Displacement does occur under the same conditions and in high yield⁷³⁸ with the 1,4-diphenoxy derivative. The latter results in quantitative yield from phenoxy-dechlorination (120°, 2 hr, phenolic phenoxide).⁷³⁸ Alcoholic hydrazine (100°, 2 hr) reacts in high yield with 1-chlorophthalazine, its 4-phenyl derivative, or 1-phenoxy analog⁷³⁹; the former reacts (80°, 30–80% yields) with various active methylene carbanions⁶⁶⁵ in benzene. Phthalazine itself and its 1,4-dichloro and 1-chloro-4-phenyl derivatives form mono- and di-phenylphthalazines with phenylmagnesium bromide (benzene, 20°, 16 hr, 50–80% yields).⁷⁴⁰

4. *Pyridopyridines (1,5-, 1,6-, 1,7-, 1,8-, 2,6-, and 2,7-Diazanaphthalenes) or Naphthyridines and Coptyrine*

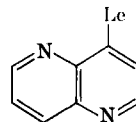
No kinetic data or semi-quantitative comparisons among themselves or with other diazines are available. The most reactive derivative is expected to be the 4-substituted-1,6-naphthyridine (**425**), with 2-substituted-1,6- and 1-substituted-2,7-naphthyridines (**426**) somewhat less reactive, all three positions being activated by two ring-nitrogens by resonance. Other positions also activated in this way



[425]



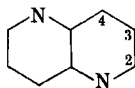
[426]



[427]

involve higher-energy resonance structures (Section IV, A), while others are activated by induction and resonance. By virtue of an accelerative *peri* effect, 4-substituted-1,5-naphthyridines (**427**) in aminations can reach the same level of reactivity as **425** and **426**, which is predicted to be that of 2-substituted quinoxalines. The potential significance of hydrogen bonding of the reagent or solvent in the behavior (cf. Sections II, B, 3 and II, C) of these azino-azines is indicated by the formation of a stable hydrogen-bonded hydrate of 1,5-naphthyridine.²⁰⁵

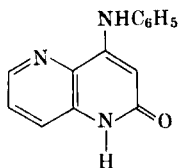
a. *1,5-Naphthyridine*. In this symmetrical diazine there are only three different ring-positions (**428**), all of which are activated both by resonance and by induction.



[428]

2-Chloro-6-methyl-1,5-naphthyridine reacts readily with methanolic methoxide (65° , 7 hr, 75% yield), but more vigorous conditions (180° , 2–7 hrs, 30–85% yield) were used for various aminations.⁷⁴¹ The 4-chlorodiazanaphthalene reacted with a *sec*-alkylamine under less vigorous conditions (95%, 36 hr, 85% yield) and with ammonia-phenol (180° , 3 hr, 50% yield) gave the phenoxy derivative which was also alkylaminated (200° , 3 hr, 90% yield).^{742a} The 3-bromo and 3-bromo-2-ethoxy derivatives of **428** were aminated with copper sulfate and concentrated ammonia (170° , 40 hr, 75% yield).^{41a, 742b}

Reaction of 2,4-dichloro-1,5-naphthyridine with ammonia (170° , 20 hr), hydrazine (100° , 16 hr), or aqueous hydrochloric acid (100° , 3 hr) was shown to yield the 2-amino- (47% yield) and 2-hydroxy-4-chloro derivatives (66% yield),⁶³¹ but 2-hydrazino substitution (68% yield) was assumed. Disubstitution with ammonia (190° , 4 hr), hydrazine (100° , 48 hr), and ammonia-phenol (180° , 6 hr) occurred in high yield.⁶³¹ Displacement of the 4-oxo group in 2,4-dioxo-1,5-naphthyridine occurs with aniline plus its hydrochloride (180° , 12 hr, 88% yield)⁶³¹ to yield **429**. Oxo groups in the 2- or 4-positions were



[429]

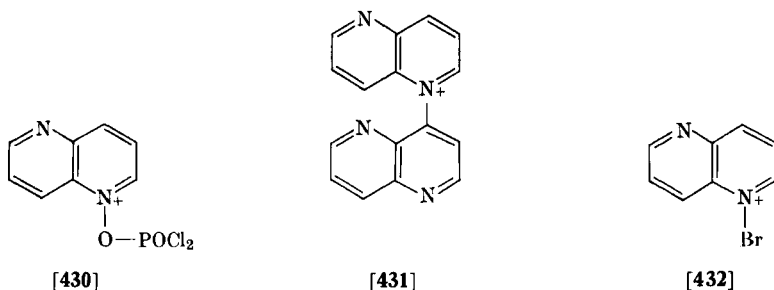
converted to 2- or 4-halogeno substituents with phosphorus oxyhalides (125° , 3 hr, 60–80% yield); the 4-chloro derivative was then aminated.^{742b}

2,6-Dichloro-1,5-naphthyridine has been only disubstituted by aqueous alkali (100° , 2 hr) or aniline (185° , 5 min).⁷⁴³ In spite of the

deactivating substituents, reactivity in 6-butoxy- and 6-methoxy-2-methyl-4-chloro-1,5-naphthyridines is sufficient for amination, *sec*-alkylamination (180° , 8 hr, 40–60% yield), hydrazination (80° , 6 hr in alcohol), and phenoxylation (160° , 3 hr, 60% yield) with phenoxide in phenol to yield 4-substitution products.⁷⁴⁴ The 4-phenoxy-6-butoxy derivative was 4-aminated with bifunctional acid-catalysis (NH_4OAc , 150° , 4 hr, 91% yield).⁷⁴⁴

The familiar pattern of 2-amination with sodamide (-33° , 90% yield)⁷⁴³ occurs also with 1,5-naphthyridine. Greater reactivity at the 2-position is attributed, as before, to a cyclic transition state with electrophilic attack at a ring-nitrogen concomitant with nucleophilic attack adjacent to the cationic center thus formed.

Nucleophilic chlorination of 1,5-naphthyridine mono- and di-*N*-oxides yields 2-chloro- and 2,6-dichloro-naphthyridines⁷⁴³ via electrophilic catalysis of the reaction of intermediates such as **430** with chloride ion. An interesting example of electrophilic catalysis is the

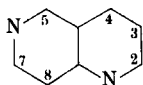


formation of **431**, which we postulate as nucleophilic substitution of hydrogen in **432** by the lone-pair of another naphthyridine molecule. The reaction proceeds rapidly⁷⁴³ with 1,5-naphthyridine and bromine in chloroform (20°). The product (**431**), which is obtained as the bromide-hydrobromide, is easily hydrolyzed (100° , 2 hr) by water autocatalytically to yield 1,5-naphthyridine and its 4-oxo derivative.⁷⁴³ The 1-methyl- and 1,5-dimethyl-1,5-naphthyridinium salts and their 3-ethyl derivatives were converted⁷⁴⁵ to the 2-oxo and 2,6-dioxo analogs by oxidative nucleophilic hydroxylation with alkaline ferricyanide (20° , < 5 hr).

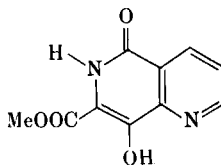
b. *1,6-Naphthyridine*. Six positions (**433**) with different activation are present in this ring system; the 2-, 4-, 5- and 7-positions are

resonance activated by both ring-nitrogens and the 3- and 8-positions are inductively activated by both azine centers.

The nucleophilic substitutions reported so far were carried out to obtain hydrazino derivatives for conversion into the unsubstituted bicyclics; dehalogenation of chloro derivatives fails due to more



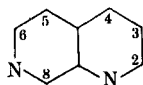
[433]



[434]

rapid hydrogenation of the azine rings. 4-Chloro-1,6-naphthyridine reacts with alcoholic hydrazine hydrate under mild conditions (20°, 4 days, 90% yield)⁷⁴⁵ as does the 5-chloro isomer (95°, 10 min, high yield).⁷⁴⁶ Nucleophilic displacement of acylated oxo groups (—O—POCl_2) by chloride ion, which produced the chloro derivatives above, proceeds with oxo or hydroxy groups in activated positions only. For example, 5-oxo-8-hydroxy-1,6-naphthyridine and its 7-carbomethoxy derivative (434) yield only the 5-chloro-8-hydroxy derivatives.⁷⁴⁷⁻⁷⁴⁹

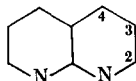
c. *1,7-Naphthyridine*. The six different ring-positions (435) are all activated by resonance by one ring-nitrogen and by induction by



[435]

the other azine center. Nucleophilic substitution of the 4-chloro derivative (376) with alcoholic hydrazine hydrate (80°, 10 min, 90% yield)^{745, 750} and of the 4-dichlorophosphoryloxy compound (from the 4-oxo derivative and phosphorus oxychloride) with chloride ion^{745, 751} has been carried out.

d. *1,8-Naphthyridine*. This symmetrical diazanaphthalene has three different ring-positions (436); the 2- and 4-positions are activated by both nitrogens by resonance and the 3-position by induction by both ring-nitrogens.



[436]

2-Chloro-5,7-dimethyl-1,8-naphthyridine reacts readily with methanolic methoxide (65° , 30 min)⁷⁵² and with other alkoxides, benzylamine, and hydrazine.⁷⁵³ 4-Chloro-7-acetamino-1,8-naphthyridine (prepared in moderate yield from the 4-oxo analog) has been alkylaminated (150° , 9 hr, 62% yield).^{742a} The degree of reactivity in 2,4-dichloro-1,8-naphthyridine⁷⁵⁴ and its 5,7-dimethyl and 3,5,7-trimethyl derivatives⁶³⁶ is such that dialkoxylation occurs readily (65° , 4 hr, 30–80% yields) via the deactivated monoalkoxy analogs (not isolated). Hydrazine hydrate (100° , 1 hr) reacts at the 2-position (70–90% yields) of 2,4-dichloro-3,5,7-trimethyl-1,8-naphthyridine and its 3- and 7-phenyl analogs.⁶³⁶ Selectivity is presumably the result of the poor resonance activation of the “4-Le-8-aza” orientation (Section IV, A, 1) relative to the “2-Le-8-aza” orientation coupled with hydrogen bonding of the reagent to the azine-nitrogen.

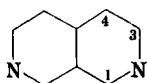
Deactivation (weak) from the adjoining ring does not prevent facile disubstitution^{755–757} of 4-methyl- and 4-phenyl-2,7-dichloro-1,8-naphthyridines with alkoxides (65° , 30 min), *p*-phenetidine (ca. 200° , 2 hr), hydrazine hydrate (100° , 8 hr), or diethylaminoethylmercaptide (in xylene, 145° , 24 hr); mono-substitution has not been reported. Nor does stronger deactivation prevent easy 2-oxonation of 5,7-dimethoxy-1-methylnaphthyridinium iodide⁷⁵⁸ with alkaline ferrieyanide via hydroxide ion attack adjacent to the positive charge and loss of hydride ion by oxidation.

e. *2,6-Naphthyridine*. No aromatic bicyclic 2,6-diazanaphthalenes are known.

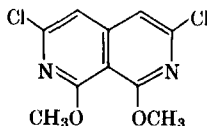
f. *2,7-Naphthyridine*. The 1956 *Ring Index* and *Chemical Abstracts* use the name copyrine for this ring system which has three different ring-positions (437). The 4-position is inductively activated by both ring-nitrogens. The 1- and 3-positions are activated by resonance, but the latter involves the unfavorable 2,3-orientation (352). 1-Substituted derivatives (426) should be one of the most reactive types of pyridopyridines.

Methoxylation of 1-chloro-3-methyl-2,7-naphthyridine occurs exothermically on addition to methanolic methoxide (20°).⁷⁵⁹ The 1-chloro or 1-chloro-3-methyl derivatives are substituted with

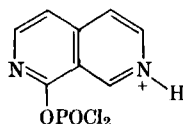
alcoholic hydrazine hydrate (80°, 10 min, 90% yield) and 2-diethyl-aminoethylamine (150°, 2 hr).⁷⁶⁰ The reactivity of the 1,3,6,8-tetrachloro derivative is increased by the chlorine substituents which will also enhance the difference between the reactivity of the 1- and 3- positions. Treatment with potassium carbonate and methanol (20°,



[437]



[438]



[439]

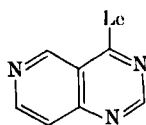
1 hr, 80% yield) produces the 1,8-dimethoxy derivative (**438**); the latter is readily converted into 3,6-dihydroxy-1,8-dioxo-1,8-naphthyridine with dilute hydrochloric acid (100°).⁷⁶¹

Nucleophilic substitutions leading to chloro compounds from the oxo analogs via intermediates such as **439** seem to be difficult, judging from the conditions used.⁷⁵⁹⁻⁷⁶¹

5. Triazanaphthalenes

Of the fourteen possible⁷⁶² triazanaphthalenes, ten are known in aromatic form, and nucleophilic displacements are reported for nine of these. Covalent hydration has been observed with 1,3,5-, 1,3,6-, 1,3,7-, 1,3,8-, and 1,4,6-triazanaphthalenes.^{614, 659}

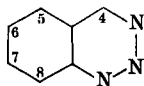
The most reactive type of triazanaphthalene derivative is expected to be **440** as discussed in Section IV, A, 1.



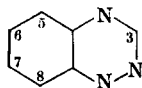
[440]

a. *Benzotriazines (1,2,3- and 1,2,4-Triazanaphthalenes)*. Considerable reactivity, as expected, is indicated by the few reported nucleophilic substitutions of 4-substituted 1,2,3-benzotriazines (**441**). Amination (alcoholic ammonia, 25°, 4 days, 60% yield) of 4-methylthio-7-chloro-1,2,3-benzotriazine⁷⁶³ proceeds readily, and alcoholic hydrazine hydrate causes evolution of methyl mercaptan immediately at room temperature with formation of the 4-hydrazino analog (25°, 16 hr,

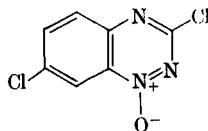
55% yield).⁷⁶³ 7-Chloro-1,2,3-benzotriazine-4-thione gives off hydrogen sulfide on treatment (20°) with alcoholic hydrazine hydrate and forms the corresponding hydrazine (80°, 3 hr, 80% yield).⁷⁶³



[441]



[442]

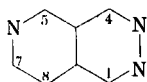


[443]

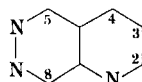
1,2,4-Benzotriazines (442) and their 1-oxides have been subjected to nucleophilic displacements. 3-Chloro-1,2,4-benzotriazine is readily converted into the hydrazino analog (95°, 2 min, 50% yield).⁷⁶⁴ The amine exchange of 3-amino-7-chloro- to 3-benzylamino-7-chloro-1,2,4-benzotriazine with benzylamine (185°, 78% yield) demonstrates the greater reactivity of the poorer leaving group in the azine ring and the much lower reactivity of the chloro group⁷⁶⁵ in the adjoining ring. When the 3,7-dichloro-1-oxide derivative (443) was heated with benzylamine (185°, 8 hr), substitution and deoxygenation occurred to give the above benzylamino compound (40% yield).⁷⁶⁵ The dichloro-*N*-oxide was easily methoxylated (65°, < 18 hr, 50% yield) and aminated (80°, 18 hr, 30–90% yield) with a variety of alkyl and aryl amines.⁷⁶⁵ Acid-catalyzed reaction with *N*-methylaniline (impurity in the dimethylaniline used) was observed⁷⁶⁵ during the preparation or isolation of 443. 3-Chloro- and 3-bromo-1,2,4-benzotriazine-1-oxides were prepared by means of phosphorus oxyhalides,⁷⁶⁴ the 3-dichlorophosphoryloxy group in the intermediates being readily displaced. 3-Chloro-1,2,4-benzotriazine-1-oxide is readily substituted with alcoholic hydrazine hydrate (80°, 1 hr, 72% yield) or with alcoholic ammonia (80°, 7 hr, 55% yield)⁷⁶⁶ and with alkoxides (65°, 1 hr) or thiourea (80°, 4 hr).⁷⁶⁴ The accelerative effect of the *N*-oxide can only be estimated; the kinetic studies of nucleophilic substitution of heterocyclic *N*-oxides are summarized in Tables II and XI (pp. 270 and 338, respectively).

b. *Pyridopyridazines*. Of the six possible⁷⁶² ring systems only two are known. 2,3,6-Triazanaphthalene (444) is known as 1-hydroxy-4-oxo derivatives.^{767–769}

1,6,7-Triazanaphthalene (445) is known as 5-hydroxy-8-oxo derivatives^{769, 770a} and as 5-phenyl-8-substituted derivatives.⁷³⁹ The 8-oxo-5-phenyl compound was converted into the 8-chloro analog⁷³⁹ via

Pyrido[3,4-*d*]pyridazine

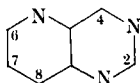
[444]

Pyrido[2,3-*d*]pyridazine

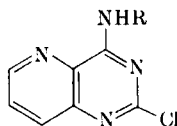
[445]

acid-catalyzed nucleophilic displacement on the 8-dichlorophosphoryloxy-5-phenyl derivative by the usual phosphorus oxychloride procedure. This chloro compound was easily converted (alcoholic hydrazine, 78°, 2 hr) into 8-hydrazino-5-phenyl-pyrido[2,3-*d*]pyridazine.⁷³⁹ Even when carefully isolated, the 5-hydroxy-8-oxo derivative of **445** gave with phosphorus oxychloride only the 8(?)-monochloro compound^{770b} which was then hydrazino-dechlorinated (120°, 30 min) in almost quantitative yield.

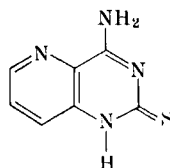
c. *Pyridopyrimidines*. Aromatic forms of the four possible⁷⁶² ring systems are known.

Pyrido[3,2-*d*]pyrimidine

[446]



[447]



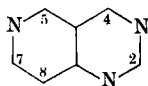
[448]

1,3,5-Triazanaphthalenes (**446**) substituted with a single leaving group have been little studied. 4-Aminopyrido[3,2-*d*]pyrimidine and its 6-methyl derivative have been hydrolyzed with 5*N* acid (100°, 30 min)^{771, 772} and 10*N* alkali (95°, 3 hr, 10% yield).⁷⁷³ Attempted replacement of the 4-oxo group (via acyloxy intermediates) with phosphorus oxychloride or pentasulfide failed,⁷¹³ in contrast to the successful replacement in the more activated 4-oxo-1,3,8-triaza analog discussed below. Similarly, the 2,4-dioxo derivative could not be thionated with the pentasulfide, and its reaction with the oxychloride was less facile⁷⁷³ than that of the 2,4-dioxo-1,3,8-triaza compound.

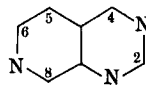
2,4-Dichloro-1,3,5-triazanaphthalene and its 6-methyl derivative react at the 4-position (70–90% yields) with ammonia in dioxane (20°, 15 min)^{771, 772} or in water (95°, 1.5 hr)⁷⁷³ and with diethylamine in dioxane (20°, 15 min).⁷⁷² The dichloroazine yields the 4-(*N*-ethyl-anilino)-2-chloro derivative under acidic conditions.⁷⁷² Amination of the 2,4-dithioxo derivative with concentrated ammonia (95°,

2 hr, 90% yield) proceeds at the 4-position to give **448**.^{772, 773} Heating the 4-amine (**447**) with aniline (185°, 30 min) gives the 2,4-dianilino analog.⁷⁷³ The 2,4-dichloroazine readily gives disubstituted products (50–95% yields) with alkoxide (65°, 5 hr),⁷⁷² ethylmercaptide (35°, 6 hr),⁷⁷² thiourea (100°, 5 min),^{772, 773} ammonia (160°, 18 hr),^{771, 773} methylamine (95°, < 1 hr),⁷⁷³ and aniline (95°, < 12 hr).⁷⁷³ On exposure to moist air the dichloro compound goes quickly to the 2,4-dioxo derivative⁷⁷² via acid-catalyzed hydrolysis.

1,3,6-Triazanaphthalene (**449**) is the most unstable of the pyrido-pyrimidines to ring-degradation at pH 2 or pH 7.7.⁶⁵⁹ The 4-oxo derivative was converted into the 4-thioxo compound⁷²⁸ via nucleophilic displacement of the acyloxy intermediate formed with phosphorus pentasulfide. The 4-carboxymethylthio-pyridopyrimidine underwent some substitution by hydroxide ion but primarily gave the ring-opening reaction, which is facilitated by resonance activation of the 2-position by the 6-aza moiety.⁷²⁸

Pyrido[4,3-*d*]pyrimidine

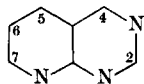
[449]

Pyrido[3,4-*d*]pyrimidine

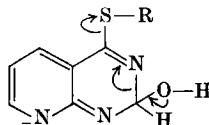
[450]

4-Oxo-1,3,7-triazanaphthalene (**450**) forms acyloxy derivatives *in situ* with phosphorus oxychloride and pentasulfide which undergo nucleophilic displacement with chloride ion and with a complex sulfide ion, respectively, to form the 4-chloro⁷⁷⁴ and 4-thioxo derivatives.⁷²⁸ The 4-carboxymethylthio compound failed to undergo the ring-opening reaction (see below) characteristic of more activated azino- and diazino-pyrimidines,⁷²⁸ but it did yield about 10% of the 4-oxo displacement product.

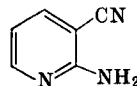
The *1,3,8-triazanaphthalene* system (**451**) has four ring-positions (the 2-, 4-, 5-, and 7-positions) activated by resonance by three

Pyrido[2,3-*d*]pyrimidine

[451]



[452]



[453]

ring-nitrogens. The most reactive one (the 4-position) is expected to be less reactive than the 1,3,6-triaza isomer (**440**), due to the "4-Le-8-aza effect" (Section IV, A, 1). The general reactivity is intermediate between that of the analogous quinazolines and pteridines.⁷⁷⁵

Only a few displacements involving mono-substituted compounds are known. 4-Chloropyrido[2,3-*d*]pyrimidine reacts readily (95°, 30 min) with aqueous aniline, hydrazine, or ammonia and with diethylamine (0°, 16 hr).⁷⁷⁵ In contrast to the 1,3,5-isomers, the 4-oxo and 2,4-dioxo derivatives are readily converted into chloro and thioxo derivatives by phosphorus oxychloride and pentasulfide.^{728, 775, 776}

2,4-Dichloro-1,3,8-triazanaphthalene under mild conditions undergoes monosubstitution at the 4-position (80–90% yields) with aqueous hydroxide (20°, 15 min), hydrosulfide (0°, 30 min), or ammonia (95°, 2 hr).^{772, 775} It is converted into di-substitution products with phenoxide, diethylamine, aniline, or hydrazine (95°, 0.1–3 hr),⁷⁷⁵ ethylmercaptide (35°, 6 hr),⁷⁷² hydrosulfide (100°, 15 min),⁷⁷⁵ ammonia in alcohol (150°, 12 hr)^{775, 776} or in phenol (185°, 3 hr),⁷⁷² or methoxide ion (65°, 5 hr).^{777a}

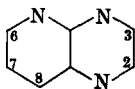
7-Aryl-5-carboethoxy (and 5-carboxy)-4-oxo-2-thioxo-1,3,8-triazanaphthalenes are converted (100°, 3 hr)^{777b} to 2-oxo compounds with chloroacetic acid (cf. **136** and **237**). The 4-oxo group is replaced (95°, 1 hr) by hydrazine along with ring-closure involving the 5-carboethoxy group; in the 2-thioxo compounds, this substituent is simultaneously converted to an oxo group.^{777b}

4-Alkylmercapto-1,3,8-triazanaphthalenes fail to substitute with aqueous sodium carbonate (100°, 20 min) but undergo a nucleophilic ring-opening instead.⁷²⁸ This reaction presumably proceeds through nucleophilic attack at the 2-position to give **452**, followed by ring-cleavage at the 2,3-bond, departure of RS[−], and formation of the easily hydrolyzed formyl derivative of the product (**453**). The reaction does not occur with 4-alkylmercaptoquinazoline or its 5- and 7-nitro derivatives nor with the 1,3,7-triazanaphthalene analog. However, it does occur when the pyrido ring-nitrogen is in the resonance-activating 6-position (4-alkylmercapto-1,3,6-triazanaphthalene) and when the nitro group is in the 6- or 8-positions of the quinazolines.⁷²⁸

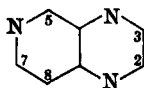
2,4-Diamino-5,6-dialkyl-7-oxo derivatives were converted with POCl₃ (105°, 45 min) to 7-chloro analogs which were then 7-thionated with hydrosulfide ion.^{777c}

d. *Pyridopyrazines*. The known nucleophilic displacements on

derivatives of these two⁷⁶² triazanaphthalenes provide little basis for comparison of their reactivity. The 6-chloro derivative of the *1,4,5-triazanaphthalene* (**454**) is converted into the 6-oxo analog by dilute acid (100°, 15 min)⁷⁷⁸ and the 8-amino group is hydrolyzed with 5*N* alkali (140°, 3 hr).⁷⁴⁹ Substituted 7-halo and 6,7-dihalo derivatives have been synthesized by ring-closure in aqueous ethanol (80°, 6 hr).^{779, 780}



Pyrido[2,3-*b*]pyrazine
[454]

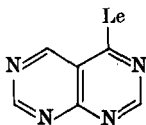


Pyrido[3,4-*b*]pyrazine
[455]

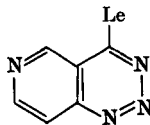
The 5-amino derivative of *1,4,6-triazanaphthalene* (**455**) is similarly hydrolyzed with 5*N* alkali (140°, 3 hr).⁷⁸¹ Covalent hydration of the 2-oxo derivative has been observed.⁷⁸²

6. Tetraazanaphthalenes

The two most reactive types of derivatives are expected to be the 4-Le-1,3,6,8- and 4-Le-1,2,3,6-tetraazanaphthalenes **456** and **457**. Of the twenty-two possible⁷⁶² ring systems, ten are known in aromatic form, and nucleophilic substitution has been carried out on only four of these. Covalent hydration has been observed in the pteridines^{614, 659} and in 1,4,5,8-tetraazanaphthalenes.



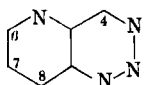
[456]



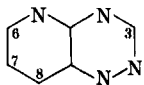
[457]

a. *Benzotetrazine*. No aromatic 1,2,3,4-tetraazanaphthalene is known.

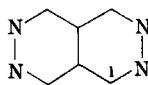
b. *Pyridotriazines*. Only two of these eight⁷⁶² bicyclo-aromatic systems are known. In *1,2,3,5-tetraazanaphthalenes* (**458**), only the ring-synthesis of the 4-oxo-3-oxide has been reported.⁷⁸³ The 3-chloro-1-oxide of *1,2,4,5-tetraazanaphthalene* (**459**) undergoes facile reaction with thiourea.⁷⁸⁴



Pyrido[3,2-*d*]-*v*-triazine
[458]



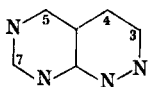
Pyrido[2,3-*e*]-*as*-triazine
[459]



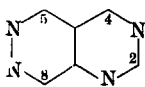
Pyridazino[4,5-*d*]pyridazine
[460]

c. *Pyridazinopyridazines*. A single derivative of only one (460) of the four possible⁷⁶² aromatic ring systems is known: 1-hydroxy-4-oxo-5,8-dimethyl-2,3,6,7-tetraazanaphthalene.⁷⁶⁹

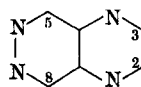
d. *Pyrimidopyridazines*. Two of the three possible⁷⁶² bicyclic azines are known, but no nucleophilic displacements have been performed on the 5,7-dioxo-3-methyl derivative⁷⁸⁵ of the 1,2,6,8-tetraazanaphthalene (461) or on the 2-amino-5-oxo-8-hydroxy derivative⁷⁶⁹ of 1,3,6,7-tetraazanaphthalene (462).



Pyrimido[4,5-*c*]pyridazine
[461]



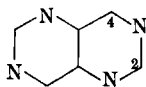
Pyrimido[4,5-*d*]pyridazine
[462]



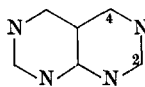
Pyrazino[2,3-*d*]pyridazine
[463]

e. *Pyrazinopyridazines*. Only the 5,8-dianisyl⁷⁸⁶ and 5-hydroxy-8-oxo derivatives^{769, 787} of 1,4,6,7-tetraazanaphthalene (463) are known, and the other possible⁷⁶² bicyclic compound is not known in aromatic form.

f. *Pyrimidopyrimidines*. Nucleophilic substitutions are known for both of the possible⁷⁶² ring systems. Stabilization of charge takes place on all four ring-nitrogens of 1,3,6,8-tetraazanaphthalenes (465) in attack of the nucleophile at the 2- or 4-positions (or the equivalent 7- and 5-positions). In the less reactive 1,3,5,7-tetraazanaphthalenes (464), two azine-nitrogens in the adjoining ring activate by induction.



Pyrimidino[5,4-*d*]pyrimidine
[464]



Pyrimido[4,5-*d*]pyrimidine
[465]

The 2,4,8-trichloro and 2,4,6,8-tetrachloro derivatives of (464) are readily trialkoxylated (alcoholic RO⁻, 20°, 4 hr, 70–90% yields),

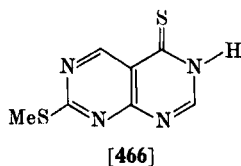
and the deactivated polyethers are still reactive enough to be hydrolyzed readily (80°, 10 min in ethanol).^{788a, 789} Heating the tetrachloro compound with ethanol (78°, 1 hr) gave 4,8-disubstitution.⁷⁸⁹ As in many other mono- and bi-cyclic azines, the 4-position is more reactive than the 2-position. 4,8-Disubstitution (90–100% yields) of the 2,4,8-trichloro and 2,4,6,8-tetrachloro derivatives also results with ammonia, alkyl- or aryl-amines in organic solvents (20°, 3 hr), ethylmercaptide or iodide ions in acetone (55°, 10 min), aqueous hydroxide (50°, 30 min), water (100°, 2 hr), and ethanol (78°, 1 hr).^{788a, 789} Dilute aqueous hydrochloric acid (100°) hydrolyzes both polychloro compounds "in a few seconds" to the trioxo and tetraoxo analogs.⁷⁸⁹ The latter also result from acid-hydrolysis (100°, 4 hr) of 2-chloro- and 2,6-dichloro-4,8-diamino-1,3,5,7-tetraazanaphthalenes.⁷⁸⁹

2,6-Bis(substituted amino)-4,8-bisethylthio(or carboxymethylthio)-pyrimido[5,4-*d*]pyrimidines (**464**) are aminated first at the 4-position with primary or secondary amines at 180° (2 hr) and then at the 8-position (200°, 4 hr).^{788b} The 4,8-bisthioxo derivative of **464** is 4,8-diaminated with ethanolamine (170°, 1 hr).^{788b} 2,6-Dianilino-4,8-dioxo(or diethoxy or dibenzyloxy) derivatives of **464** react at the 4- and 8-positions with primary or secondary amines at 180°. The 2,4,6,8-tetrachloro derivative is claimed to go to the tetrakis(triethylammonio) compound.^{788b}

All types of nucleophilic substitution occur more readily with 1,3,6,8-tetraazanaphthalene (**465**) derivatives than with the 1,3,5,7-tetraaza isomers. Thionation of oxo derivatives proceeds quite readily (80°, 45 min),^{728, 790, 791a, 791b} but reaction with phosphorus oxychloride (difficult with oxo derivatives of **464**) would probably fail due to acid-catalyzed ring-cleavage.⁷⁹² The nucleophilic ring-opening discussed above (**452** forming **453**) occurs even more readily with 4-methylthio- or 4-carboxymethylthio-1,3,6,8-tetraazanaphthalenes and aqueous sodium carbonate (20°, 2 hr) or bicarbonate (100°, 10 min).⁷²⁸ No displacement takes place and 4-amino-5-cyanopyrimidine (50–85% yields) is formed. A tendency to ring-opening is characteristic of derivatives of this ring system (**465**), especially when an unsubstituted "2"-position is present. For example, dilute acid or aqueous ammonia gives ring-cleavage of 2-ethylthio-5-oxo-1,3,6,8-tetraazanaphthalene but 2-substitution of the 2-ethylthio-5,7-dioxo analog.^{791b} Both can be aminated with *alcoholic* ammonia (160°, 20 hr)^{791b} or piperidine (110°, 6 hr).^{791a}

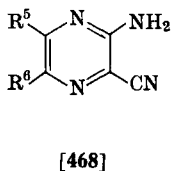
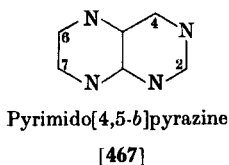
A displacement of the 4-methylthio group can be achieved with

formamidine acetate in 2-ethoxyethanol (135°, 20 min)⁷⁹³ to give the 4-amino derivative of **465**. The same displacement and yield result with the 4-thioxo group also.⁷⁹³ Competitive displacement in the 2,5-bismethylthio pyrimidopyrimidine **465** with alcoholic benzylamine (20°, 15 hr) produces 5-substitution (85% yield).⁷⁹⁰ This behavior again illustrates the greater reactivity of "4"- over 2-positions in azines. Another illustration is the reaction at the "4"-position in the 2-methylthio-5-thione derivative **466** with aqueous



benzylamine (100°) or methylamine (100°, 30 min),⁷⁹⁰ even though the thione group is generally the poorer of the two leaving groups. This group also shows good reactivity in the 2-benzylamino-5-thioxo bicyclic, which undergoes 5-alkylation with alcoholic *n*-propylamine (130°, 4 hr).⁷⁹⁰ The high reactivity of derivatives of ring system **465** is indicated by the fact that appreciable hydrolysis of many of the amino derivatives occurs on recrystallization from water.⁷⁹⁰

g. *Pyrimidopyrazine or Pteridine*. Pteridine (**467**) represents the only possible⁷⁶² fusion of pyrazine and pyrimidine rings. Due to its



electron-attracting nature, it is quite unstable to acidic or alkaline nucleophilic cleavage of the pyrimidine ring, especially when the 2-position is unsubstituted.⁷⁹⁴ This tendency is decreased by the presence of electron-donating substituents but is an underlying characteristic of pteridine chemistry. Some "substitution" reactions are believed to be actually a ring-opening and reclosure sequence^{795, 796} (cf. ref. 48 for such a sequence in purines), e.g., facile displacement of amino and thioxo groups. With the 6-chloro and 6-oxo

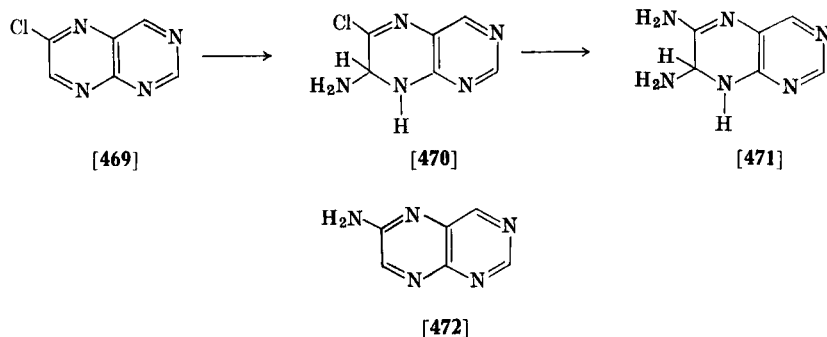
derivatives, decomposition of the ring by highly reactive sulfur nucleophiles supersedes nucleophilic substitution.⁷⁹⁷ In other cases also, ring-cleavage supersedes or accompanies substitution. In attempted displacement of 4-methylthio or 4-carboxymethylthio groups with hydroxide ion (100°, 6 min),⁷²⁸ the pyrimidine ring is opened and 2-amino-3-cyano(5,6-substituted)-pyrazines (**468**) are obtained along with only small amounts of the displacement product.⁷²⁸ Covalent hydration has been observed^{614, 659} in various pteridine derivatives; it is postulated below that the relative reactivity of the ring-positions is altered due to the intervention of covalent adducts such as **470** or its 3,4-dihydro isomer.

A kinetic study or semi-quantitative comparison of the reactivity of the mono-chloropteridines has not been reported. To autocatalytic hydrolysis with water, 4-chloropteridine reacts readily in the cold; the 6-isomer is somewhat less reactive; and the 2-chloro derivative requires brief boiling. The last is readily hydrolyzed by dilute acid.^{798, 799} 7-Chloropteridine self-quaternizes on standing or in solution at 50° and reacts rapidly with methanolic methoxide (65°, < 1 hr).⁷⁹⁷ The 6-chloro isomer (**469**) is easily substituted (55–80% yields) with methanolic methoxide (20°, 30 min), ammonia in benzene (20°, 1 hr), or methanolic dimethylamine (20°, 4 hr).⁷⁹⁸ The 4-chloro derivative is more reactive than the 2-chloro isomer toward water (pH 6, 100°), methanolic methoxide (20°, 1 hr), aqueous hydrosulfide (95°, 2 hr), or alcoholic ammonia (20°, 15 min).^{800a} With the latter reagent, the 2-chloro compound gives no reaction at 80°. ^{800a} 2-Amino-4-alkylthio(or aralkylthio)pteridines undergo facile nucleophilic substitution^{800b} at the 4-position with hydrosulfide, alkylmercaptide, or hydroxide ions and with hydrazine, in spite of the deactivating effect of the 2-amino group.

Reactivity in this ring system is sufficient for facile hydrolysis (20°, 2 hr or 100°, 1 min) of the 2-, 4-, 6-, and 7-methoxypteridines^{794, 797} in high yield and for easy substitution (75–90% yields) of the 7-methylthio group with methanolic hydrazine hydrate (65°, 15 min), dimethylamine (65°, 30 min), and ethanolic ammonia (125°, 6 hr).⁷⁹⁷ The 7-acyloxy intermediate in thionation of 7-oxopteridine with phosphorus pentasulfide is readily substituted (80°)⁷⁹⁷ to form pteridine-7-thione. The chloro group in 6-aryl-2,4-diamino-7-chloropteridine still reacts^{800c} readily with hydrazine (100°, several minutes) in spite of the two deactivating amino substituents.

The high reactivity of various 6-substituted pteridines is postulated

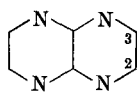
as due to prior intervention of covalent addition [Eq. (12)] of the nucleophile or the solvent. Such nucleophilic addition probably occurs also in poly-substituted compounds and accounts for the 6,7-disubstitution of trichloro and tetrachloro derivatives.⁸⁰¹ 6-Amino- and 6-dimethylamino-pteridines are very rapidly hydrolyzed (to 6-oxo)



by cold 0.01*N* hydrochloric acid, while the 2- and 4-isomers require brief boiling^{798, 799} with acid or 0.01*N* alkali (100°, 3 min). The 6-oxo group in 2-aminopteridine-4,6-dione and related compounds is replaced (65–100°, 3 hr, 80% yield) by alkoxy groups using acidic alcohols.^{248b}

The 4-amino group in 2,4-diaminopteridine is preferentially displaced by 6*N* acid hydrolysis (100°, 30 min).⁸⁰² Greater reactivity at the 4-position occurs also with 2,4-dichloro-6,7-dimethylpteridine and alcoholic ammonia (20°, 1 hr, 55% yield).^{800a} 2,4,6,7-Tetrachloropteridine with aqueous alkali (20°) or liquid ammonia (–70°, rapidly) gives 6,7-disubstitution (92% yield of the diamine).⁸⁰¹ Reaction via a covalent adduct such as 470 or its 3,4-dihydro isomer presumably explains this anomalous result which is not in keeping with the relative activation in bicyclo-aromatics. Charge stabilization in the transition state and the kinetic data in Section IV, A, 2 would indicate a reactivity sequence of 4- > 2- > 7- > 6-position for mono-substituted pteridines. Actually, the substitution reactions indicate the sequence 7- > 4- > 6- ≅ 2-position, with the reactivity of the 7- and 6-isomers varying with the significance of prior covalent additions. The sequence of progressive substitution of tetrachloropteridine does not give the relative reactivity in mono-substituted pteridines^{803, 804} due to the unequal activating effects of the chlorines and to the unequal deactivating effects of the groups introduced (cf. Section II, E).

h. *Pyrazino*[2,3-*b*]*pyrazine*. Only polymethyl derivatives of this 1,4,5,8-tetraazanaphthalene (**473**) are known.⁸⁰⁵

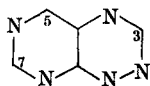


[473]

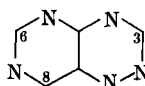
7. *Pentaaza-, Hexaaza-, and Heptaaza-naphthalenes*

Only three of the fourteen possible⁷⁶² pentaazanaphthalenes are known, and none of the ten possible⁷⁶² hexaazanaphthalenes or two possible⁷⁶² heptaazanaphthalenes are known in aromatic form.

5,7-Dioxo derivatives of **474** are known,⁸⁰⁶⁻⁸⁰⁸ as well as 5-chloro-1,2-dihydro-1-methyl-3-oxo-1,2,4,6,8-pentaazanaphthalene.⁸⁰⁹

Pyrimido[5,4-*e*]-*as*-triazine

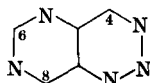
[474]

Pyrimido[4,5-*e*]-*as*-triazine

[475]

5-Amino-3-alkyl derivatives of **474** have been prepared and found to undergo facile nucleophilic 5-substitution with methanolic hydrazine (65°, 4 hr, 75% yield), hydroxide ion (20°, 3 hr, 75% yield), or propanolic benzylamine (100°, 5 hr, 80% yield).⁸¹⁰ The first two reactions may proceed by a ring-opening and reclosure sequence.⁸¹⁰

The 3-amino-8-oxo derivative of 1,2,4,5,7-pentaazanaphthalene (**475**) is known^{811a} as well as various 3-substituted derivatives^{811b} of the 6,8-dioxo compound. The 3-methylthio- and 3-ethylthio-6,8-dioxo derivatives and their 7-methyl and 5,7-dimethyl analogs were prepared^{811b} by ring-closure. 3-Ethylthiopyrimido[4,5-*e*]-*as*-triazine-6,8-dione was 3-substituted with alkali (2*N*, 100°, > 30 min) or acid (2*N*, 100°, < 2 hr, 70% yield) and with ammonia, aniline, piperidine, or monoalkylamines (in pyridine, 115°, 4 hr, 75-85% yield).^{811b}

Pyrimido[5,4-*d*]-*v*-triazine

[476]

6,8-Dioxo-5,7-dialkyl-3-oxides of **476** have been synthesized by ring-closure and converted by means of thionyl chloride (20°, 6 hr) into the 6,8-dioxo-5,7-dialkyl-4-chloro derivatives of 1,2,3,5,7-pentazaphthalene.⁸¹² The 4-chloro derivative was unstable to acid-catalyzed hydrolysis (20° in moist solvent for several hours or boiling 1.5*N* HCl for 1 min) yielding a 3:1 ratio of substitution (4-oxo analog) and of ring-opening (to 1,3-dialkyl-5-diazoniopyrimidine-2,4,6-trione). Its high reactivity is indicated by its very facile methoxylation (0°, 15 min, 65% yield). The structure of the 6,8-dioxo-3-oxide⁸¹³ of **476** had been incorrectly assigned.⁸¹²

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$$k = (C_{\text{Boltzmann}}/C_{\text{Planck}}) T e^{st/R} e^{-\Delta H^\ddagger/RT}$$

which has nearly the same form as the Arrhenius equation, where A is proportional to ΔS^\ddagger and where $E_A = \Delta H^\ddagger$ within the usual experimental error.

- 482 The entropy of activation, ΔS^\ddagger , can be calculated from the above equation in the form $\Delta S^\ddagger/2.303R = \log k_{\text{rate}} - 10.753 - \log T + (E_A/2.303RT)$ using the second as the unit of time, E_A obtained as above, and $R = 1.987 \text{ cal deg}^{-1}$.

- The free energy of activation, ΔF^\ddagger , is related to the heat (or enthalpy) of activation, ΔH^\ddagger and ΔS^\ddagger , by the equation $\Delta F^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$.
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